Asymmetric alkylation of substituted -keto esters

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ASYMMETRIC ALKYLATION OF SUBSTITUTED β-KETO ESTERS

Submitted by Anne Hodgson

for the degree of Ph.D.

of the University of Bath

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To my parents, for their

constant love and support

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Finally, I am grateful to Glaxo Group Research and the SERC for a CASE award.

ABSTRACT

This thesis is introduced by a review of the methods available for the asymmetric alkylation of β-keto esters.

Two methods have been investigated for the asymmetric alkylation of β-keto esters.

(i) Alkylation of β-keto esters incorporating a chiral alcohol as a chiral auxiliary gave diastereoselectivities of up to 70% but revealed serious problems associated with the ambident nature of β-keto ester enolates.

(ii) A detailed study of the allylic anions of β-keto ester enamines showed that these anions can be alkylated selectively at the α-position. Enantioselectivities of up to 15% were observed on incorporating (S)-2-methoxymethylpyrrolidine into the enamine.

The synthesis of C_2-symmetric amines, 2,5-dimethylpyrrolidine and 2,5-bis(methoxymethyl)pyrrolidine is described and the problems associated with the preparation of enamines of these amines are discussed.

The preparation of the tricyclic skeleton of the benzenoid analogue of huperzine A and huperzine B *via* a β-keto ester alkylation and an intramolecular radical cyclisation strategy and model studies towards the synthesis of huperzine B are described.

CONTENTS

ABBREVIATIONS

The following abbreviations are used in the text;

Ac	acetyl
acac	acetylacetonate
AChe	acetylcholinesterase
AIBN	azobisisobutyronitrile
Bn	benzyl
b.p.	boiling point
br	broad
Bu	butyl
cat	catalyst
mCPBA	meta-chloroperoxybenzoic acid
DBU	1,8-diazabicyclo[5.4.0.]undec-7-ene
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
de	diastereomeric excess
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMSO	dimethylsulphoxide
DMPU	1,2-dimethyl-2-oxohexahydropyrimidine
ee	enantiomeric excess
equiv	equivalent
g.c.	gas chromatography
h	hours
hfc	3-(heptafluoropropylhydroxymethylene)-(+)-camphorato
HMPA	hexamethylphosphoramide
HMPT	hexamethylphosphorous triamide
HSAB	hard and soft acid and base

i.r.	infra red
LDA	lithium diisopropylamide
LIS-NMR	lanthanide induced shift-nuclear magnetic resonance
M^+	molecular ion
min	minutes
m.p.	melting point
Ms	methanesulphonyl
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
OTf	triflate, trifluoromethylsulphonate
PCC	pyridinium chlorochromate
py	pyridine
rt	room temperature
SAMP	(S)-1-amino-2-methoxymethylpyrrolidine
TCDI	thiocarbonyldiimidazole
THF	tetrahydrofuran
TLC	thin layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
Ts	p-toluenesulphonyl
Δ	heat
δ	chemical shift

1. INTRODUCTION

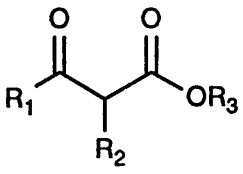
THE ASYMMETRIC SYNTHESIS OF SUBSTITUTED β-KETO ESTERS

1.1 INTRODUCTION

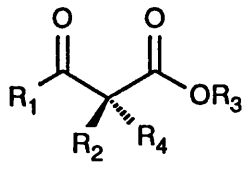
The generation of quaternary carbon centres continues to represent a significant challenge in organic synthesis. In recent years, the enantioselective construction of quaternary carbon centres has been the focus of much effort resulting in a number of approaches to this problem[1]. This review will concentrate on the advances made in the asymmetric synthesis of substituted β-keto esters.

β-Keto esters are useful synthetic intermediates and β-keto esters containing a chiral centre at the α-position are valuable starting materials in natural product synthesis.

α-Monosubstituted β-keto esters (**1**) cannot retain enantiomerically pure form as enoliziation rapidly leads to racemisation.



(1)



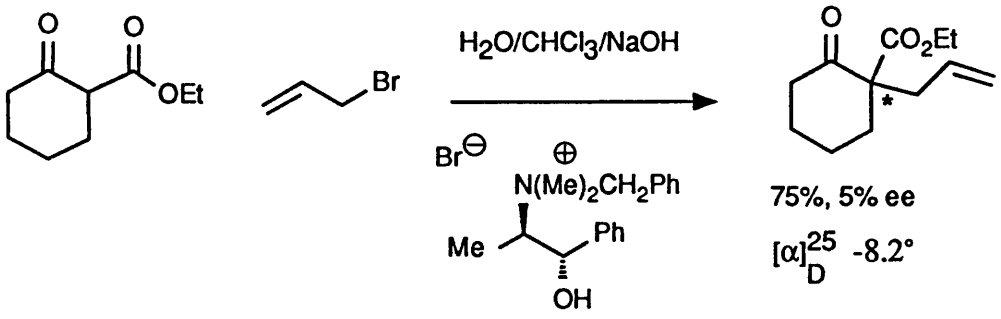
(2)

However, α,α-disubstituted β-keto esters (**2**) are optically stable. Hence, the asymmetric synthesis of these β-keto esters requires the formation of a chiral quaternary carbon centre.

Many of the strategies adopted use either an alkylation reaction or Michael addition as the key carbon-carbon bond formation step and much of the early work concentrated on catalytic procedures.

1.2 ASYMMETRIC ALKYLATION VIA CHIRAL PHASE TRANSFER CATALYSIS

The earliest attempts to effect enantioselective alkylation of β-keto esters involved the use of a chiral phase transfer catalyst. In 1975, Fiaud[2] reported an asymmetric alkylation reaction using (-)-N-benzyl-N-methylephedrinium bromide (3) as the catalyst. (Scheme 1).



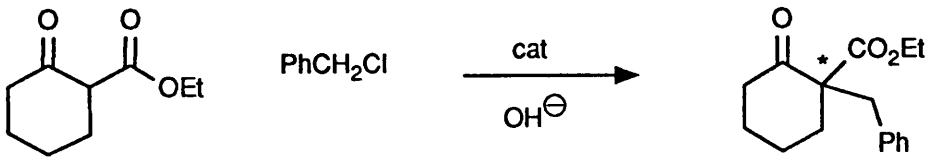
(3)

Scheme 1

The reaction yielded optically active products and in one case, the enantiomeric excess was measured, by lanthanide chiral shift induced nmr techniques (LIS-NMR), to be 5%.

Saigo and coworkers[3] investigated benzyl [*cis*-2-hydroxymethylcyclohexyl] dimethylammonium bromide (4) as a chiral phase transfer catalyst. (Scheme 2).

The alkylated product was formed in good yield and found to be optically active. By comparison of the specific rotations with those obtained by Fiaud[2], Saigo considered the catalyst (4) to be as effective a chiral catalyst as the ephedrine derived catalyst (3) but more advantageous as both enantiomers were readily available.



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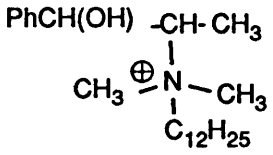
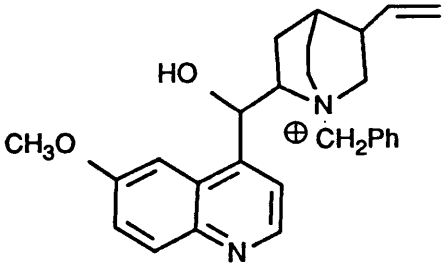


(5)

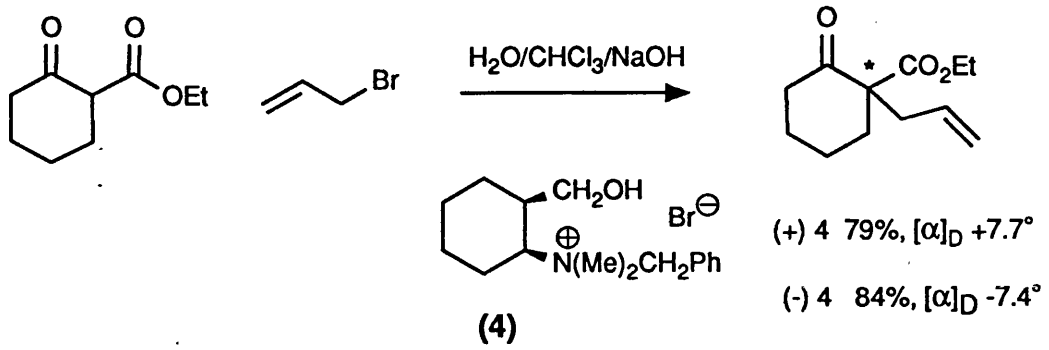
40%, $[\alpha]_D$ -3.6°, 7% ee



(6)

35%, $[\alpha]_D$ -4.5°

Scheme 3



Scheme 2

Juliá studied asymmetric alkylation using chiral quaternary ammonium salts derived from ephedrine (**5**) and china alkaloids (**6**).[4] (Scheme 3)

Although optically active products were obtained, only low levels of asymmetric induction were measured (7% by LIS-NMR).

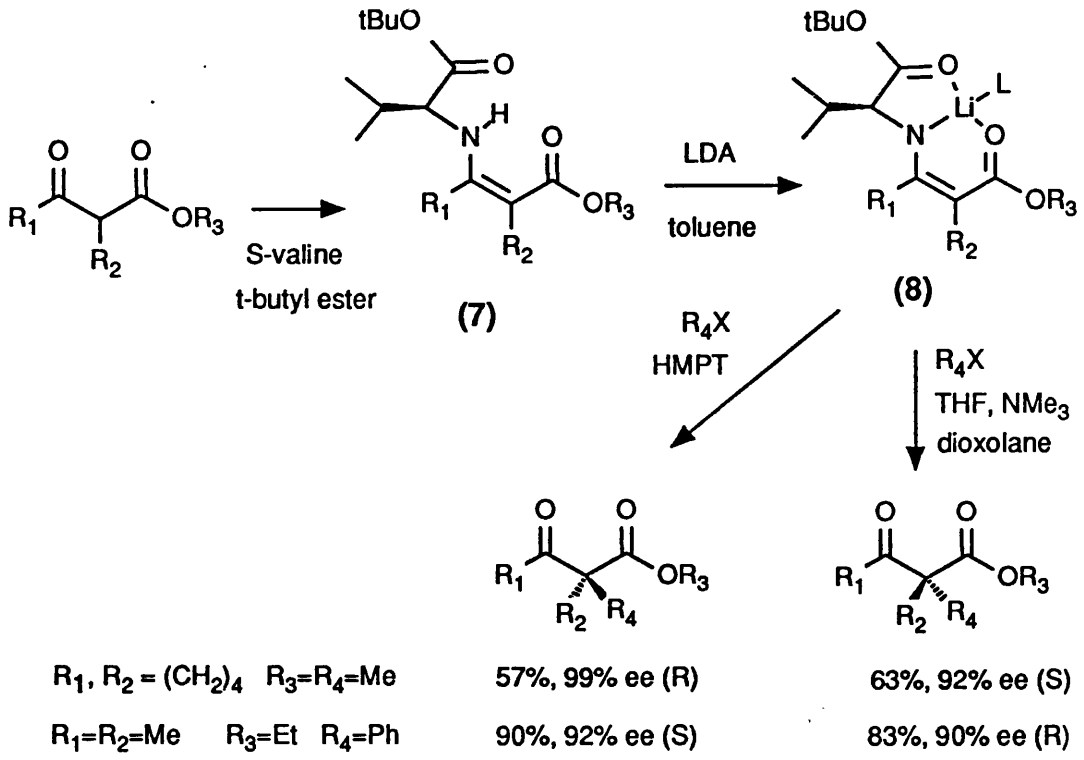
A range of chiral phase transfer catalysts have been investigated as catalysts for the asymmetric alkylation of β-keto esters but the levels of asymmetric induction observed are low (less than 10%). This does not represent a synthetically useful approach to the problem.

1.3 ASYMMETRIC ALKYLATION VIA LITHIOENAMINES

Koga and coworkers have studied the diastereoselective alkylation of chiral lithioenamines derived from α-alkyl-β-ketoesters.[5] This was an extension of their earlier work on the asymmetric alkylation of enamines derived from simple ketones.[6]

Enantiomerically pure chiral enamines (**7**) were prepared from the corresponding β-keto esters and S-valine *tert* butyl ester. These chiral enamines were then

lithiated with LDA in toluene and subsequent alkylation and hydrolysis yielded the disubstituted β-keto esters in good chemical and optical yields. It was found that the addition of a cosolvent had a profound effect on the stereochemical course of the reaction. (Scheme 4).



Scheme 4

An opposite sense of asymmetric induction was observed in the toluene-HMPT solvent system on one hand and toluene-THF, dioxolane or trimethylamine on the other, with the former always exhibiting a higher degree of selectivity. The reaction is general for a range of cyclic and acyclic β-keto esters with a range of electrophiles.

The factors controlling the diastereofacial selectivity in this reaction are not well understood but a possible rationale has been published.[7] The addition of HMPT to the lithioenamine **(8)** resulted in an acceleration of the rate of reaction and an

enhancement of diastereofacial selectivity. Koga has suggested that on addition of HMPT, the lithioenamine (existing as a mixture of aggregates in toluene) is converted to an organised reactive species bearing HMPT as a ligand for the lithium cation. (Figure 1).

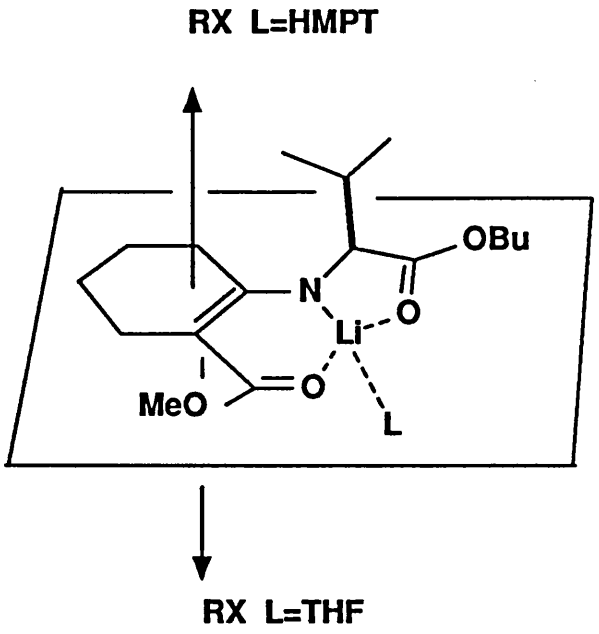
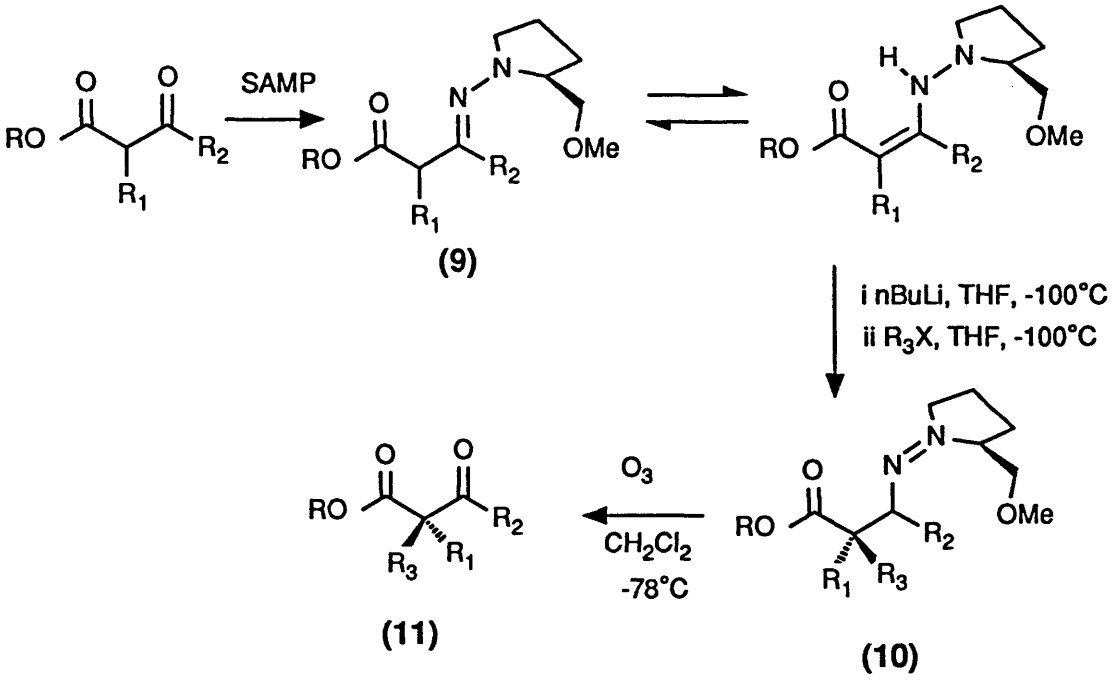


Figure 1

Assuming that the electron pair on nitrogen remains in conjugation with the enamine double bond, the bulky and strongly ligating HMPT would coordinate to lithium and, as a result, increase the negative charge in the enamine system and suppress bottom side attack, hence, attack occurs from the top face.

A more weakly ligating ligand, an ether or amine, can also convert the aggregates to a reactive species (Figure 1) but it cannot activate the enamine system enough to react with the alkyl halide. Attack occurs from the less sterically hindered bottom side of the anion.

Although further studies are required for a fundamental understanding of the



R_1,R_2 = $-(CH_2)_3-$, R = R_3 = Me 60% ee

R_1 = R_2 = Me, R = Et, R_3 = nC_3H_7 31% ee

Scheme 5

factors controlling the diastereofacial selectivity, this method represents a powerful method for the preparation of β-keto esters with high enantiomeric purity and has been used by other groups to prepare these esters as synthetic intermediates.[8]

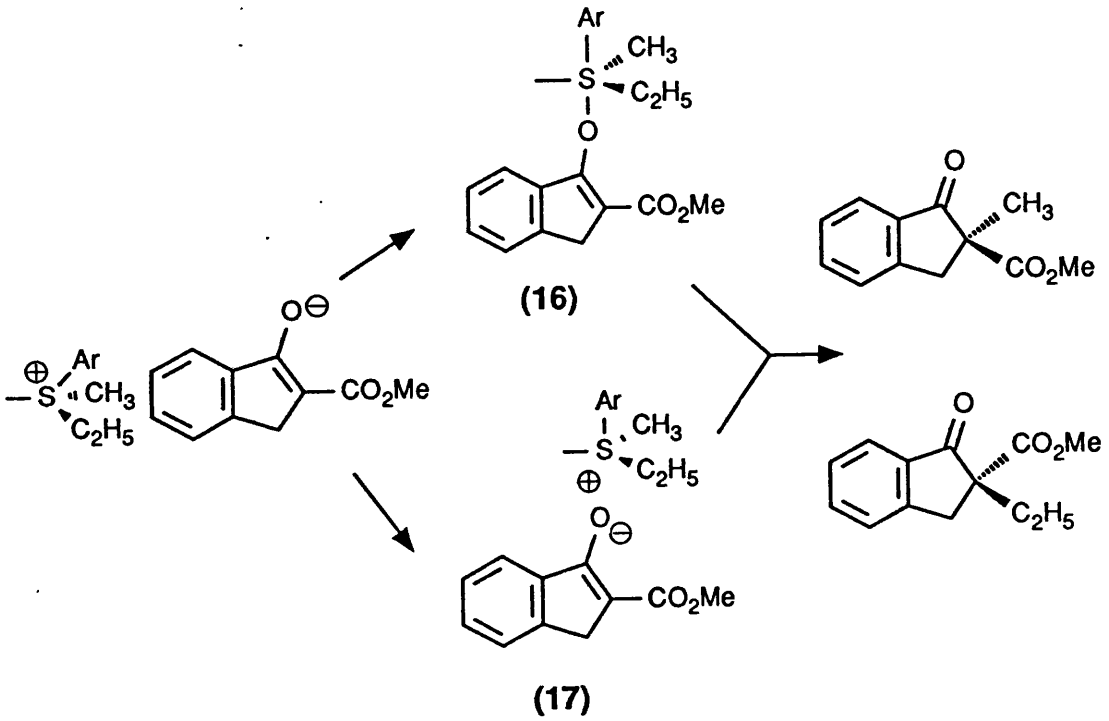
Enders has applied his SAMP/RAMP hydrazone technology to the preparation of chiral β-ketoesters.[9] (Scheme 5).

Cyclic and acyclic β-keto esters are easily transformed to the corresponding hydrazones (**9**). Metalation with *n*-butyllithium followed by trapping with an alkyl halide and subsequent oxidative cleavage of the hydrazone (**10**) leads to optically active β-keto esters (**11**). Although the chemical yields are good, the level of enantiomeric excess observed is not yet as high as with the hydrazones of simpler carbonyl compounds.

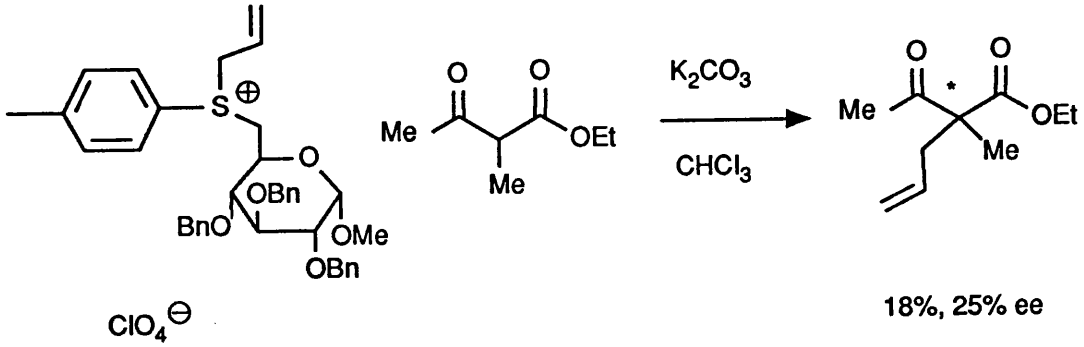
1.4 ASYMMETRIC ALKYLATION VIA OPTICALLY ACTIVE SULPHONIUM SALTS

Matsuyama and Kobayashi have explored the asymmetric alkylation of β-keto esters with optically active sulphonium salts as the electrophile.[10] Alkylation of β-keto esters with aryldialkylsulphonium salts leads to the formation of four products. (Scheme 6).

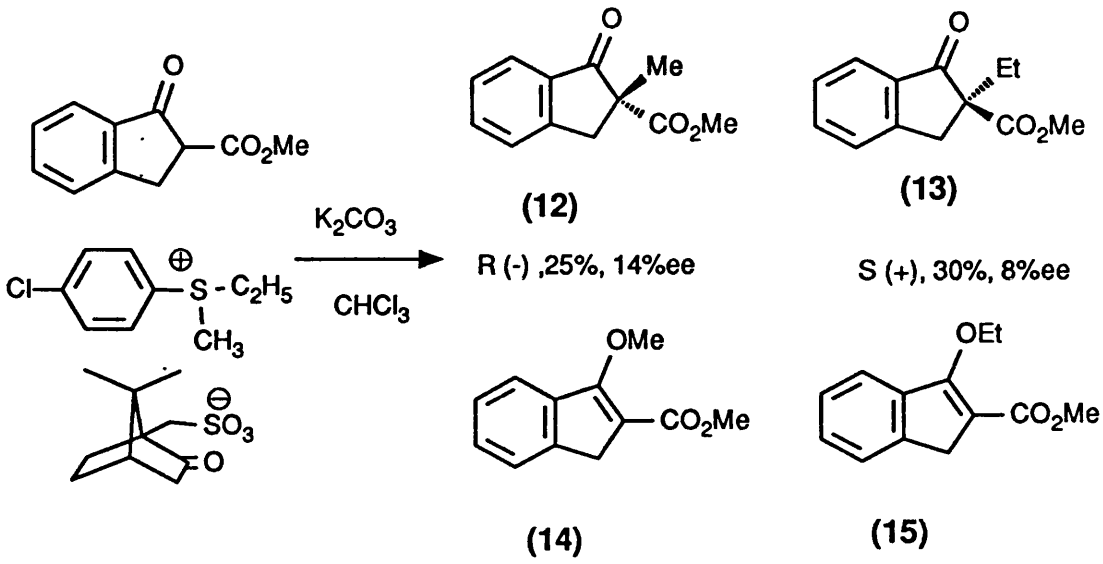
When dialkylsulphonium salts are used as alkylating agents, two products can be formed arising from transfer of either alkyl group. The reaction with β-keto ester anions is further complicated by the ambient nature of the anion allowing alkylation at both carbon and oxygen sites. In Scheme 6, although the C-alkylated products (**12**) and (**13**) are the major products, significant amounts of O-alkylated products (**14**) and (**15**) are formed. Interestingly, it was observed that



Scheme 7



Scheme 8



Scheme 6

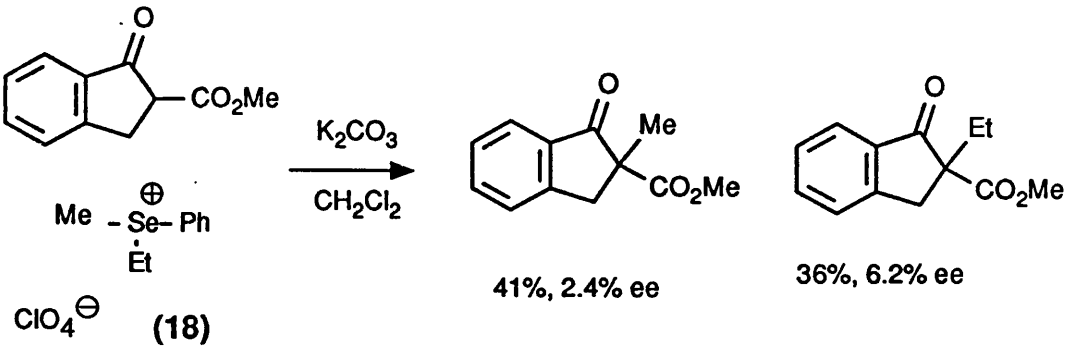
the C-methylated product (**12**) and C-ethylated product (**13**) have opposite configurations and were formed in almost equal amounts. These results suggest that the reaction did not proceed *via* an S_N2 mechanism but was postulated to involve an S-O sulphurane intermediate (**16**) or tightly-bound ion pair (**17**). (Scheme 7).

The use of chiral dialkylsulphonium salts as alkylating agents resulted in low levels of asymmetric induction (up to 15% ee). However, an enantiomeric excess of 25% was observed when using an alkylsulphonium salt containing a carbohydrate moiety.[11] (Scheme 8).

The authors assumed that the asymmetric induction was due to the steric bulk of the carbohydrate group and showed that alkylation now proceeds *via* an S_N2 mechanism.

Low levels of asymmetric induction were observed in alkylation reactions using optically active selenonium salts (**18**).[12] The absolute configuration of the salts

was deduced from the absolute configuration of the products obtained by analogy with the results obtained using sulphonium salts. (Scheme 9).

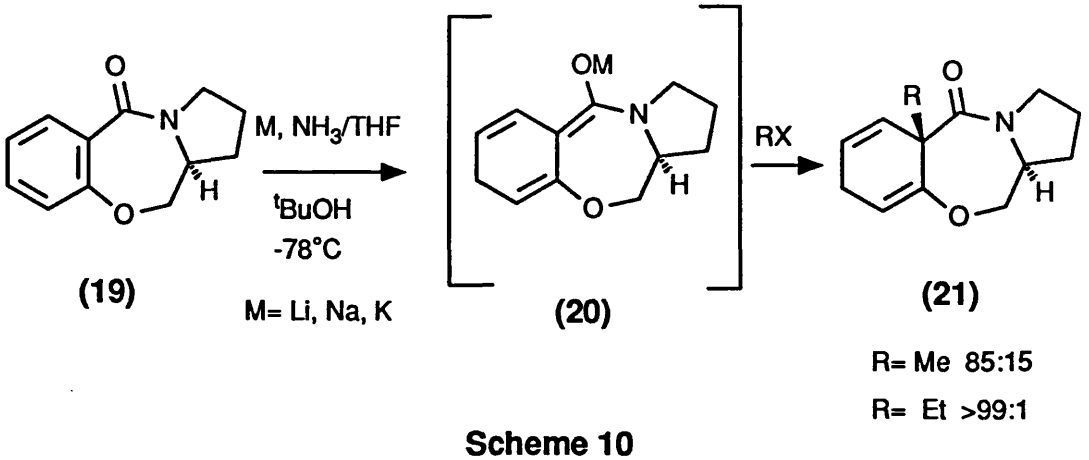


Scheme 9

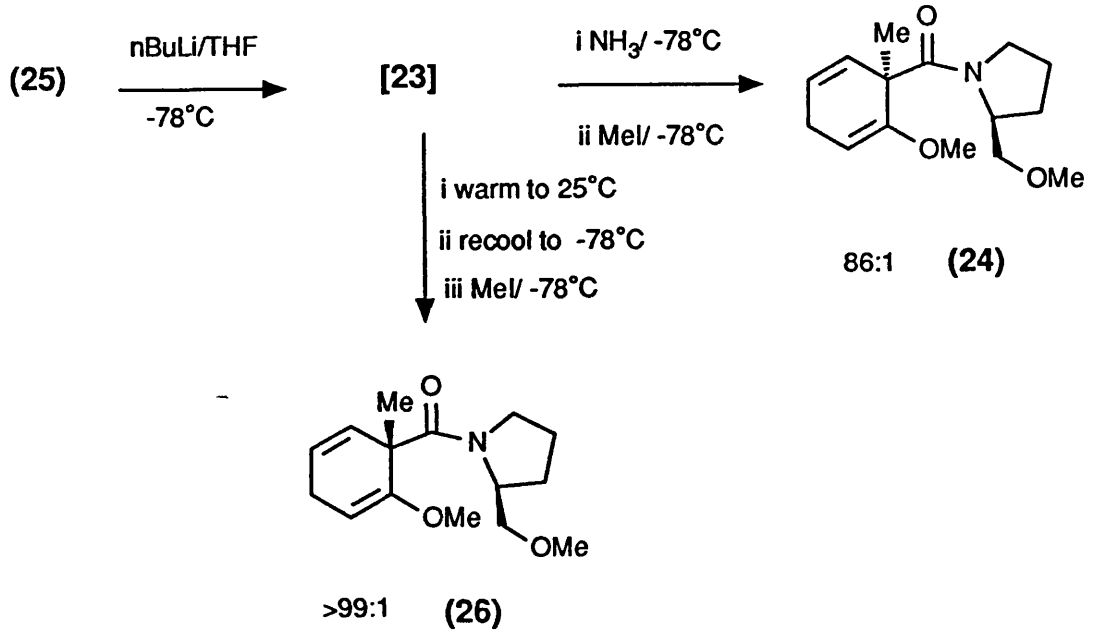
1.5 REDUCTIVE ALKYLATION OF AROMATIC CARBOXYLIC ACID DERIVATIVES

An elegant method for the preparation of enantiomerically pure chiral cyclohexanes has been developed by Schultz.[13]

The reductive alkylation of chiral benzoxazepinone **(19)** by an alkali metal in ammonia-THF solution at -78°C followed by trapping of the resulting amide enolate **(20)** with an alkyl halide gave the alkylated product **(21)** with high diastereoselectivity. (Scheme 10).

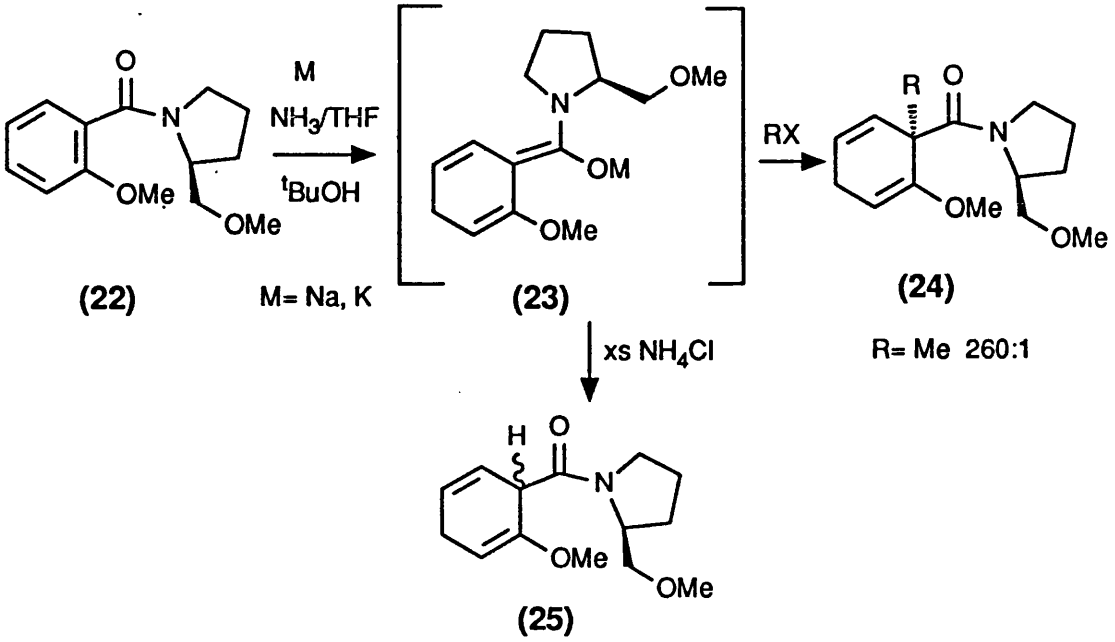


Scheme 10


(25)
nBuLi/THF
-78°C
[23]
i NH3/ -78°C
ii MeI/ -78°C
Me
O
N
OMe
OMe
86:1
(24)
i warm to 25°C
ii recool to -78°C
iii MeI/ -78°C
Me
O
N
OMe
OMe
>99:1
(26)

Scheme 12

Reductive alkylation of the chiral benzamide (22) gave an alkylated product (24) with the opposite sense of absolute configuration at the newly formed centre *via* an amide enolate (23). (Scheme 11).



Scheme 11

Further investigation[14] revealed that both R and S configurations were available from benzamide (22). Reaction of the enolate (23) with excess ammonium chloride gave the 1,4-cyclohexadiene (25). Deprotonation of (25) reformed the enolate (23) and by careful choice of conditions either product (24) or (26) could be prepared. (Scheme 12).

The origin of the diastereoselectivity can be rationalised by a consideration of the enolate structures in solution but this can only be regarded as a model until more knowledge of the enolate structures in solution can be obtained.[14]

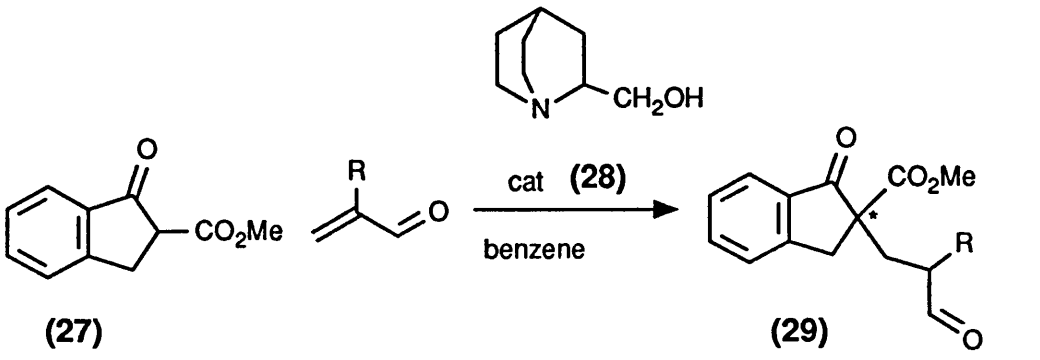
In summary, from a single chiral auxiliary, l-prolinol, products of high enantiomeric purity in either R or S configurations can be obtained. The 2-alkoxybenzoic acid derivatives are masked β-keto esters. Hence, this methodology allows access to enantiomerically pure

2-oxo-cyclohexanecarboxylates. Schultz has applied this methodology to prepare enantiomerically pure β-keto esters as intermediates in natural product synthesis.[15]

1.6 CHIRAL CATALYSTS IN THE MICHAEL REACTION

The Michael addition reaction is a powerful method of carbon-carbon bond formation and the stereochemical aspects of Michael addition have been reviewed recently.[16] Several approaches to chiral β-keto esters have been investigated using the Michael reaction.

The classic conditions for performing Michael additions involve the use of a catalytic amount of base in a protic solvent. Langstrom and Bergson[17] were the first to examine the possibility of enantioselective Michael addition by use of a chiral non-racemic base. Reaction of methyl 2-carboxy-1-indanone **(27)** with acrolein or isopropylacrolein in the presence of 2-hydroxymethyl quinucline **(28)** as the catalyst yielded optically active products **(29)**. However, they did not report the degree of asymmetric induction. (Scheme 13).



R= H $[\alpha]_{546}$ +8.83°

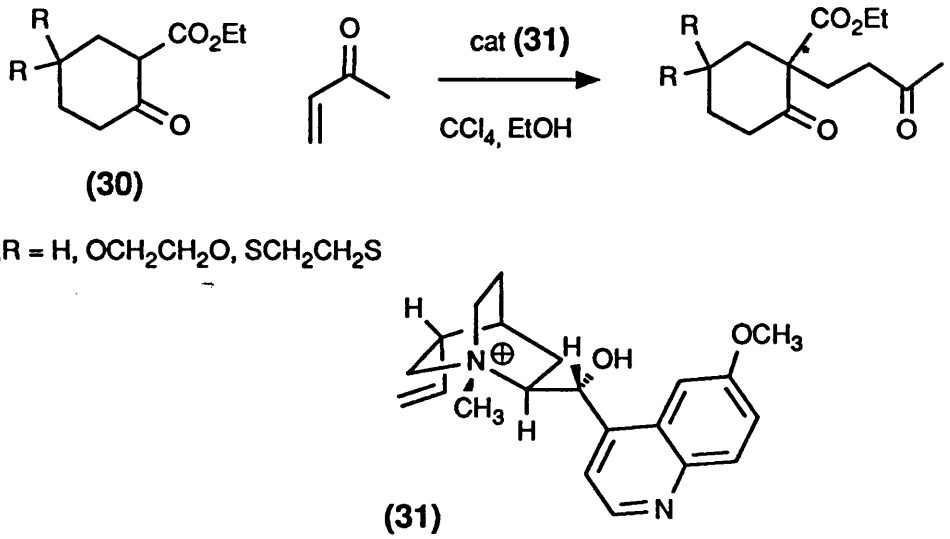
R= -$CH(CH_3)_2$ $[\alpha]_{546}$ +28.4°

Scheme 13

This report proved to be the spur for other groups to investigate the potential for enantioselective Michael addition.

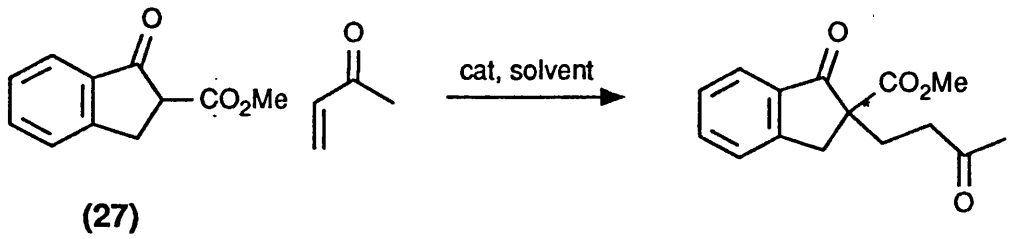
Wynberg and coworkers undertook a systematic study of Michael additions of β-keto esters with cinchona alkaloids as catalysts.[18]

Michael addition of the cyclohexanone derivatives **(30)** required the use of quinine methohydroxide **(31)** as catalyst (Scheme 14). An enantiomeric excess of up to 25% was obtained.



Scheme 14

The cinchona derivative **(27)** underwent Michael addition with methyl vinyl ketone in the presence of cinchona alkaloids (Scheme 15). Selectivities of up to 76% (entry 1, Table 1) were obtained. As the enantiomers of the naturally occurring cinchona alkaloids (for example **(32)**) are not readily available, the alkaloid **(33)** was used as the catalyst to allow access to Michael adducts of the opposite configuration (entry 2).

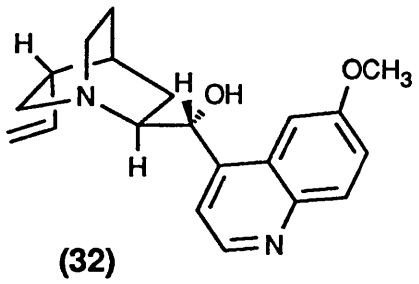


(27)

Scheme 15

entry	cat	solvent	yield	ee	ref
1	(32)	CCl_4/ EtOH, -21°C	99%	76%(S)	18
2	(33)	CCl_4/ EtOH, -21°C	100%	69%(R)	18
3	(34)	Toluene, rt	92%	42%(R)	19
4	(35)	Toluene, rt	61%	27%(S)	20

Table 1



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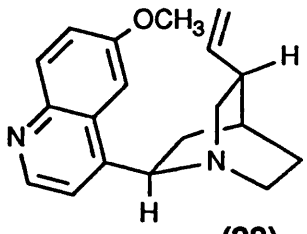

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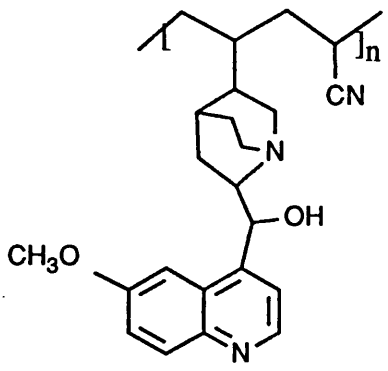

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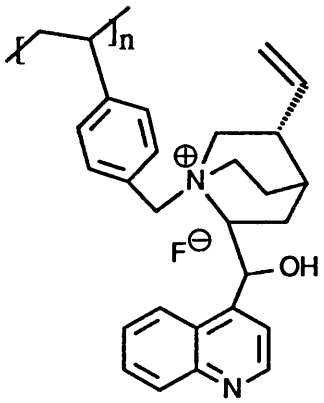


(35)

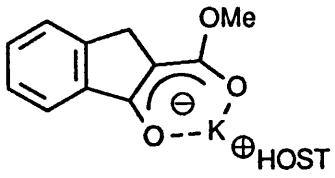
It was found that the highest levels of asymmetric induction were observed at low temperature and the amount of ethanol present in the reaction mixture was critical to success. The hydroxy group of the alkaloid was also shown to be crucial in obtaining high selectivities.

A problem associated with the use of alkaloids as catalysts is the relative difficulty of separating the product β-keto ester from the catalyst. A solution to this problem has been to attach the catalyst to a polymer support and Kobayashi[19] has prepared copolymers of cinchona alkaloids and acrylonitrile (for example **(34)**). These materials are efficient catalysts for the Michael addition (entry 3, Table 1), but the level of asymmetric induction with the polymer bound alkaloids is lower than with the unbound catalyst.

Polymer-supported chiral quaternary ammonium salts derived from cinchona alkaloids have also been prepared.[20] These also catalyse the addition of methyl vinyl ketone to indanone **(27)** but with low chemical yield and enantiomeric excess of up to 27%, (entry 4, Table 1).

Cram has reported the use of chiral crown complexes as catalysts in Michael reactions obtaining very impressive levels of asymmetric induction.[21] Reaction of indanone **(27)** with methyl vinyl ketone in the presence of the catalyst obtained by complexing potassium bases to chiral host **(36)** can give optical yields close to quantitative. (Scheme 16).

The two faces of the planar carbanion, ion paired to the complexed potassium ion **(37)** were differentiated by the chiral binaphthyl barrier. The approach of the electrophile from the open face gives the product **(38)** of essentially one configuration,[22] illustrated schematically in Figure 2.



(37)

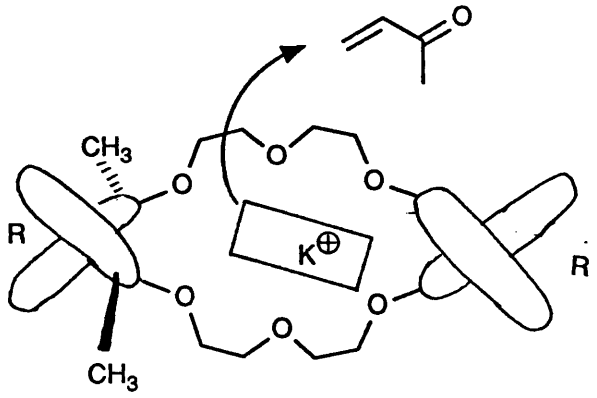
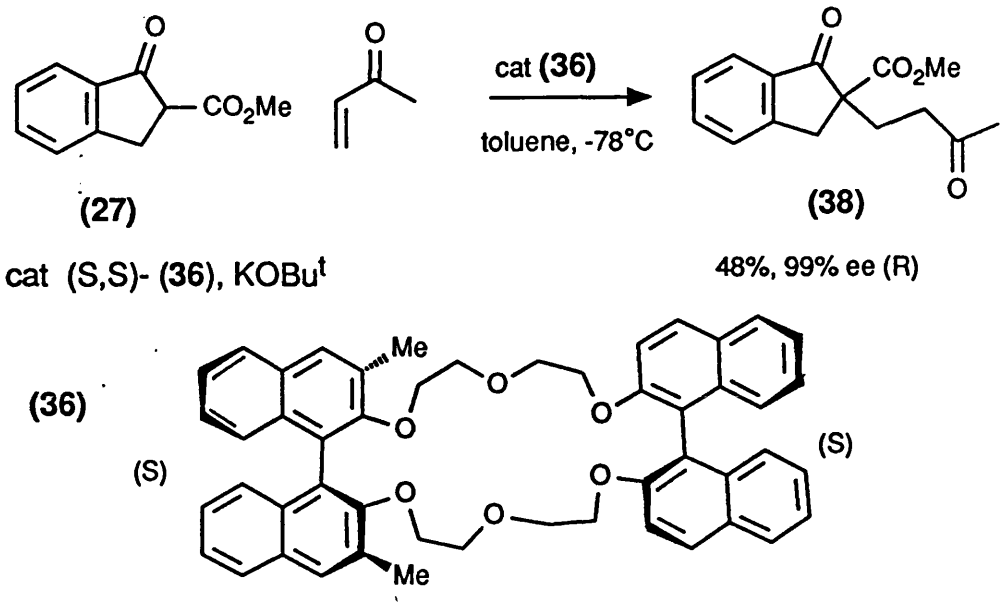
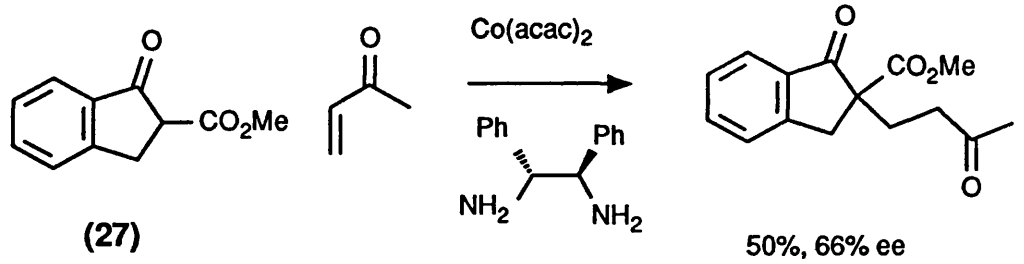


Figure 2



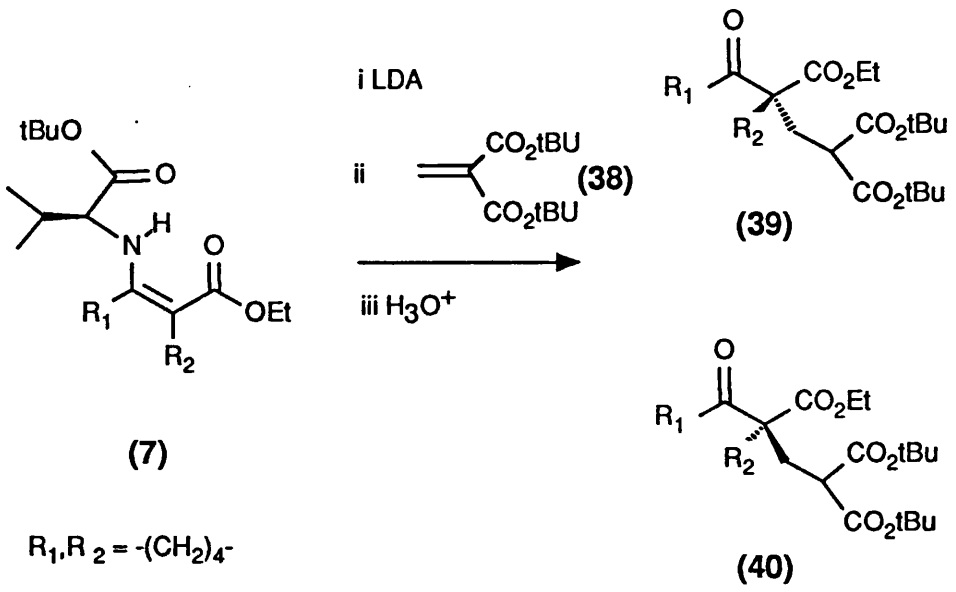
Scheme 16

Brunner and Hammer[23] have investigated a transition metal catalyst for enantioselective Michael additions. An enantiomeric excess of up to 66% was observed in the reaction of indanone (27) and methyl vinyl ketone with a catalyst system derived from $Co(acac)_2$ and 1,2-diphenyl-1,2-ethanediamine. (Scheme 17).



Scheme 17

It is assumed that an asymmetric cobalt-amine species is the active catalyst in the reaction. It was found that $Co(acac)_2$ efficiently catalyses the reaction while the diamine alone slowly catalyses the reaction with low asymmetric induction (6% ee).



Scheme 18

entry	solvent	additive	temp	product	yield	ee
1	toluene	HMPA	-95°	(39)	73%	92%(S)
2	toluene	THF	-95°	(40)	87%	76%(R)
3	THF	none	-105°	(40)	86%	95%(R)
4	toluene	none	-78°	(40)	59%	33%(R)

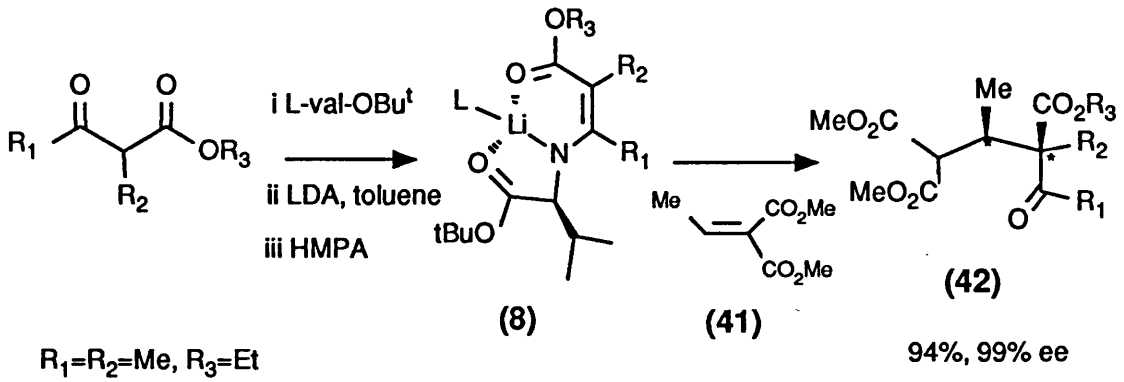
Table 2

1.7 ASYMMETRIC MICHAEL REACTIONS VIA CHIRAL ENAMINES

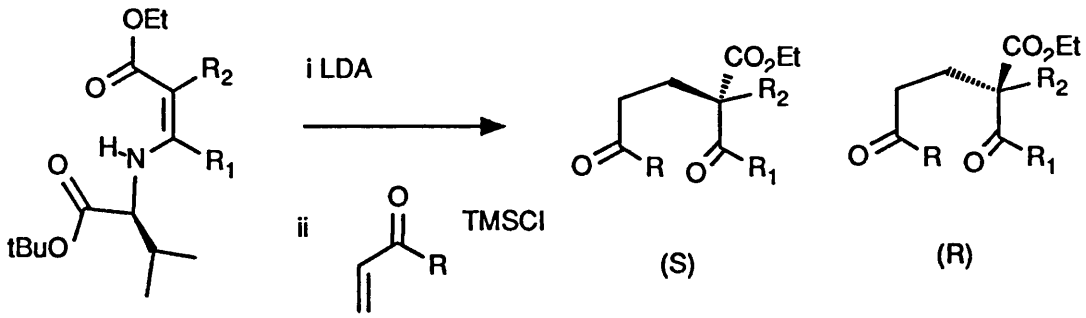
Koga and coworkers have studied the asymmetric Michael reaction of chiral enamines (**7**) with di-*tert*-butylmethylenemalonate (**38**)[24] (Scheme 18).

Generation of the lithioenamine in toluene and addition to malonate (**38**) gave the product (**40**) in 33% ee (entry 4, Table 2). As observed in the alkylation reactions of lithioenamines,[5] addition of a cosolvent had a profound effect on the stereochemical course of the reaction. Addition of HMPA reversed the sense of asymmetric induction (entry 1). The highest selectivities (up to 95% ee) were observed when THF was used as the solvent (entry 3). Koga postulated that the results would be explained by invoking the chelated structure of the lithioenamine (Figure 1) as for alkylation reactions.

Reaction of the lithioenamine (**8**) with methylidene malonate (**41**) in toluene at -78°C with HMPA as a cosolvent gave the adduct (**42**) as the sole product[25] (Scheme 19). This provides a method for the creation of contiguous quaternary and tertiary carbon centres.



Scheme 19



$R_1,R_2 = -(CH_2)_4-$, R = Me

solvent	T	yield	ee
THF	-100°	67%	90% (R)
toluene-HMPA	-95°	48%	60%(S)

Scheme 20

This process is general for enamines of cyclic and acyclic β-keto esters. The high enantio- and diastereoselectivity can be explained by considering the intermediate structure (Figure 3).

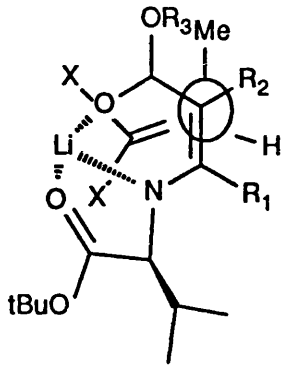


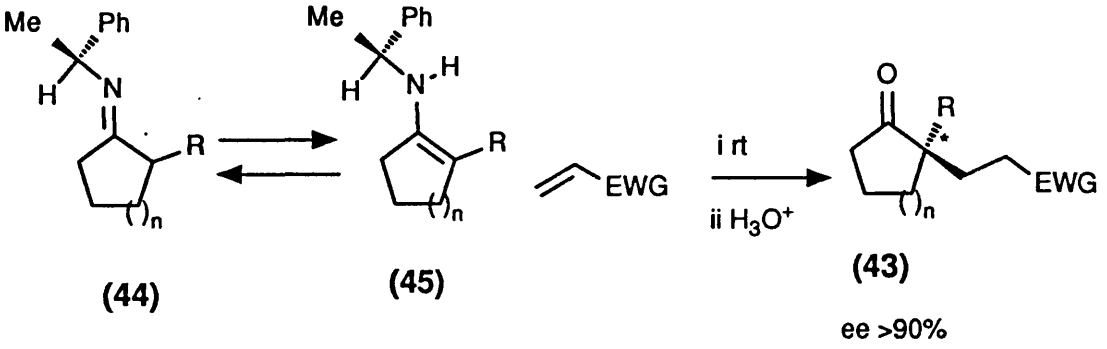
Figure 3

The reagent **(41)** will attack the lithioenamine from the α-face due to coordination of a carbonyl group to lithium placing the methyl group in the least sterically demanding position.

A disadvantage of this methodology is that the chiral enamines will only react with activated Michael acceptors. To improve the scope of the procedure to facilitate reaction with non-activated Michael acceptors, a number of Lewis acids were screened as activators.[26]

Chlorotrimethylsilane promoted the asymmetric Michael reaction of chiral enamines of α-alkyl-β-keto esters with useful Michael acceptors producing either enantiomer with good selectivity depending on the choice of solvent system (Scheme 20).

Cycloalkanones (**43**) bearing an α-quaternary carbon centre can be prepared with high stereoselectivity from chiral cyclic imines (**44**) *via* their reactive enamine form (**45**)[27] (Scheme 21).

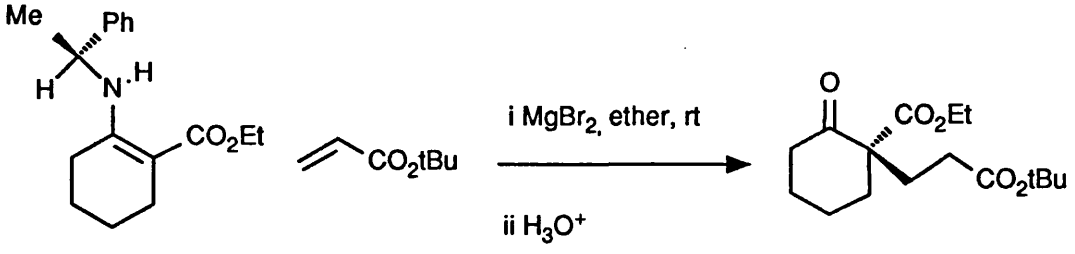


(**44**) (**45**) (**43**)

ee >90%

Scheme 21

This methodology has now been extended to allow the preparation of substituted β-keto esters *via* β-enaminoesters[28] . (Scheme 22)

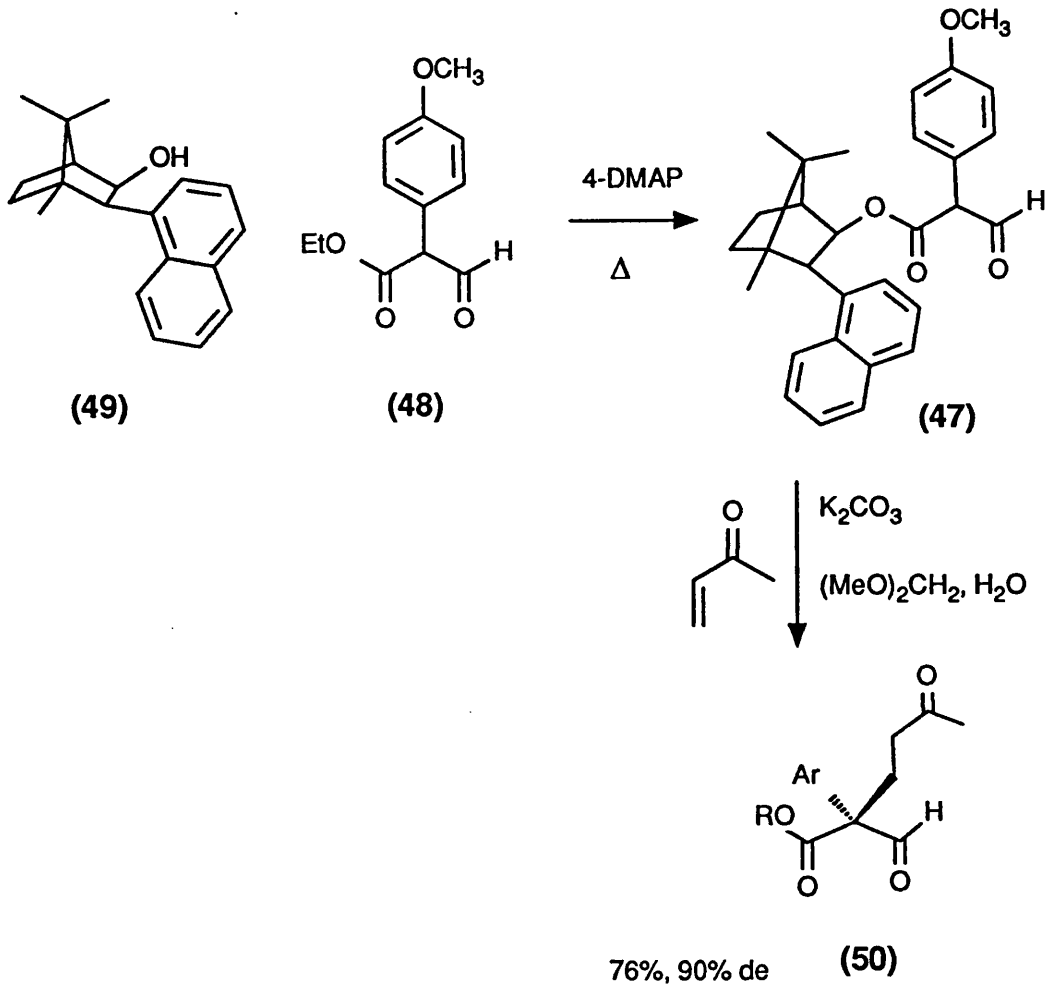


(+)- (**46**)

60%, 90% ee (S)

Scheme 22

Reaction of the enaminoester (**46**) with *t*-butyl acrylate took place at room temperature in ether with high asymmetric induction (up to 90%). Magnesium bromide was found to be the most effective Lewis acid for mediating the addition. The major enantiomer formed (S absolute configuration at the newly formed centre) is the one resulting from attack on the face opposite the phenyl group in enamine (+)-(**46**).[46]

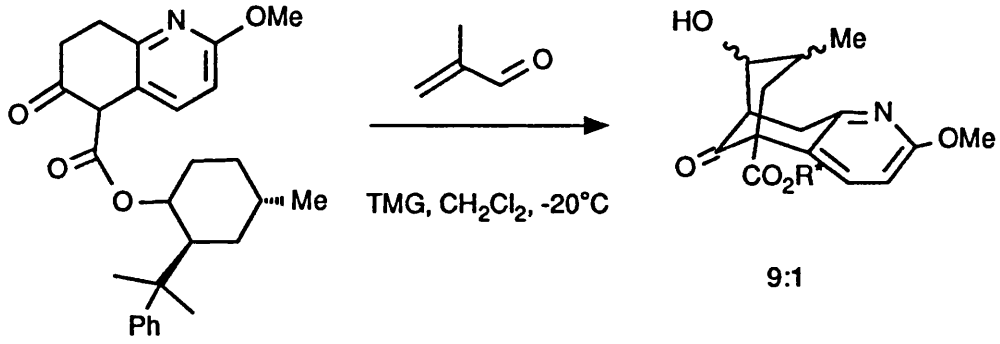

OH
OCH3
EtO
H
O
O
4-DMAP
Δ
OCH3
O
O
O
H
(49)
(48)
(47)
O
K2CO3
(MeO)2CH2, H2O
O
Ar
RO
H
O
O
76%, 90% de
(50)

Scheme 23

1.8 ESTER BOUND CHIRAL AUXILIARIES IN THE MICHAEL REACTION

Taber has developed an enantiomerically pure Michael donor (**47**) for use in a natural product synthesis.[30] The ester (**47**) was prepared by transesterification of α-formyl ester (**48**) with chiral alcohol (**49**) derived from camphor. Michael reaction of the ester (**47**) with methyl vinyl ketone gave the product (**50**) with a diastereomeric excess of 90% (Scheme 23). The adduct (**50**) was then elaborated to the enantiomerically pure mesembrane alkaloid (+)-O-methyljoubertiamine.

Kozikowski employed a Michael addition to a chiral β-keto ester in an enantioselective synthesis of (-)-huperzine A.[31] Tandem Michael aldol reaction of the 8-phenylmenthol ester (**51**) with methacrolein provided the bridged intermediate (**52**) with a diastereomeric ratio of 9:1 (Scheme 24).

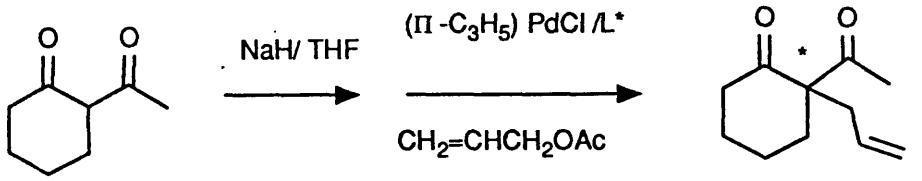


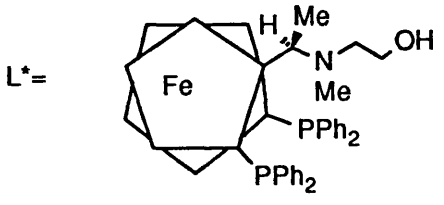
(**51**)

9:1

(**52**)

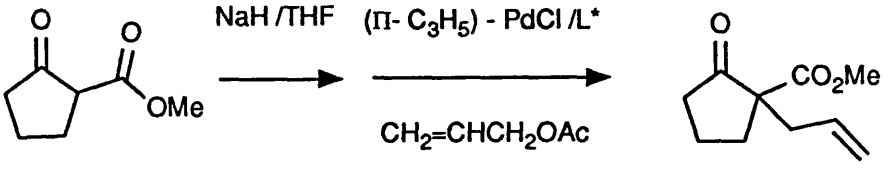
Scheme 24





(53)

Scheme 26

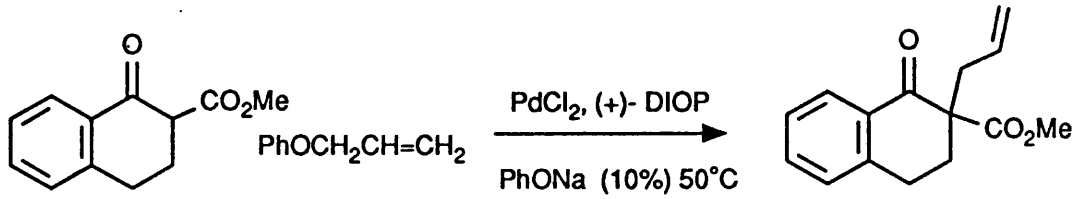


L* = **(53)**

Scheme 27

1.9 PALLADIUM CATALYSED ALLYLATION OF β-KETO ESTERS

In 1978, Kagan and coworkers reported the enantioselective catalytic transfer of an allylic group of an allylic ether or ester to β-dicarbonyl compounds.[32] (Scheme 25).



68%, 10% ee

Scheme 25

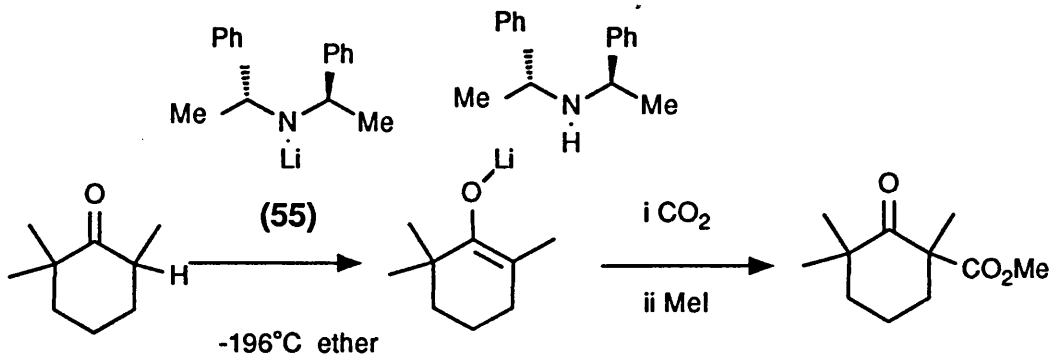
β-Diketones and β-keto esters were cleanly alkylated under the reaction conditions. The palladium catalyst can be either a Pd^{II} complex, a chiral phosphine and a basic cocatalyst or a Pd^{0} complex and a chiral phosphine. The levels of asymmetric induction were low (generally less than 20%).

In 1988, Hayashi[33] demonstrated the use of chiral ferrocenyl phosphine ligands in the palladium catalysed allylation reaction with active methine compounds. In the reaction of allylacetate with the sodium enolate of 2-acetylcyclohexanone, asymmetric induction up to 81% can be achieved dependent on the ligand (Scheme 26).However, the ligand (**53**) was not very effective for the allylation of β-keto esters (Scheme 27).

This methodology provides a route for the asymmetric allylation of β-diketones but efficient asymmetric allylation of β-keto esters may require further structural modification of the chiral phosphine ligand.

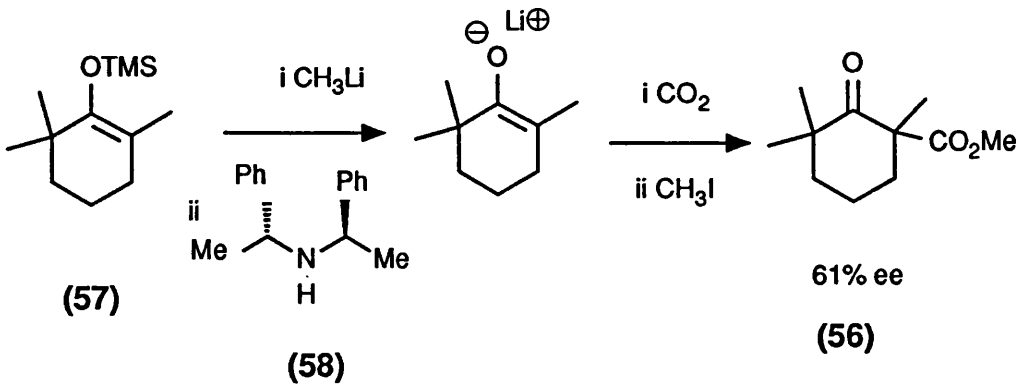
1.10 β-KETO ESTER SYNTHESIS VIA ENANTIOSELECTIVE CARBOXYLATION

An alternative strategy for the preparation of chiral β-keto esters has been suggested by Hogeveen and Menge.[34] Deprotonation of the ketone (54) by a chiral lithium amide base (55) generated an enolate which was trapped with carbon dioxide to afford the β-keto ester (56) in 67% ee. (Scheme 28).



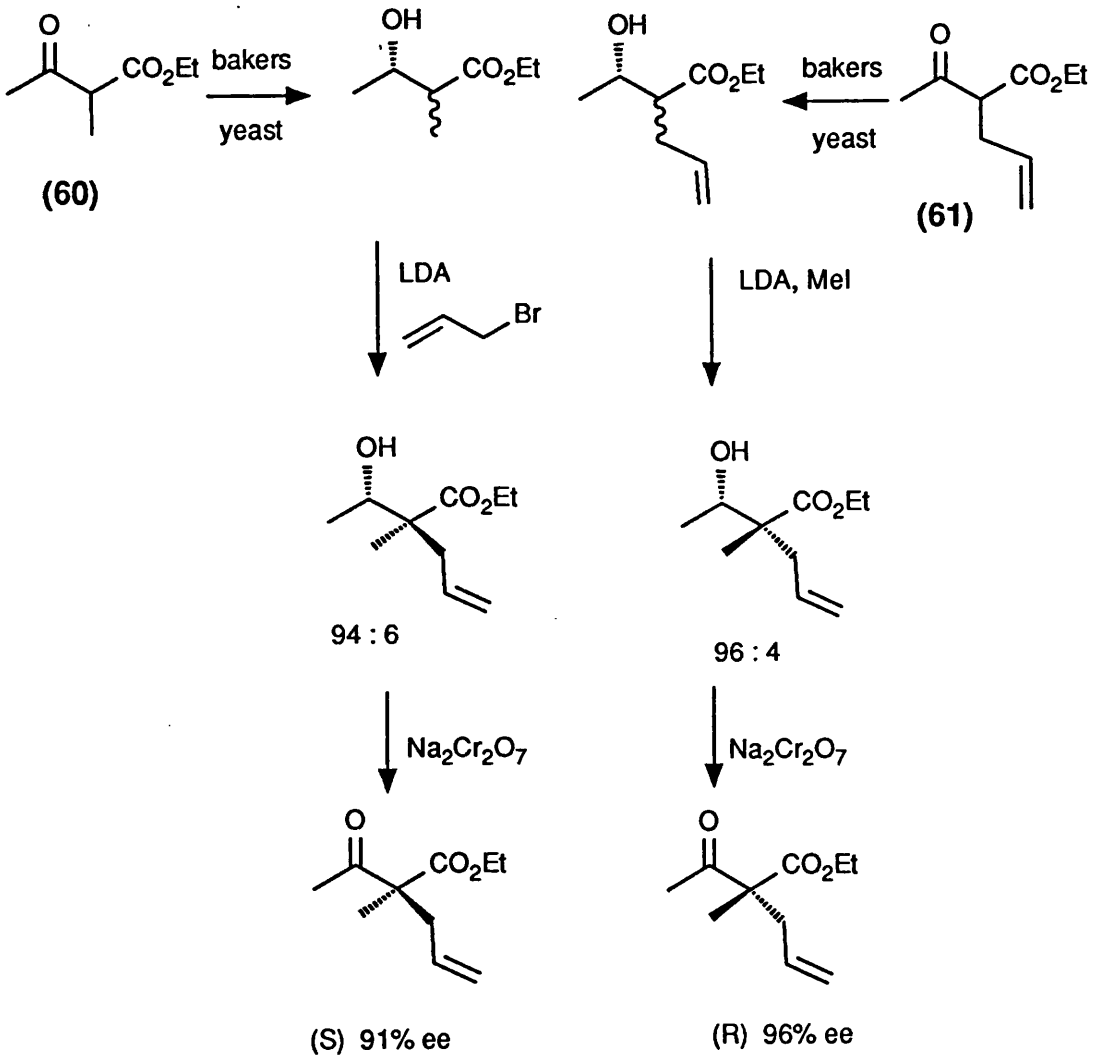
Scheme 28

Interestingly, it is possible to obtain the β-keto ester (56) with 61% ee from the silyl enol ether (57) and methyllithium in the presence of chiral amine (58). (Scheme 29).



Scheme 29

The chiral amine (58) can act efficiently as a chiral ligand for inducing enantioselectivity in carboxylation reactions.

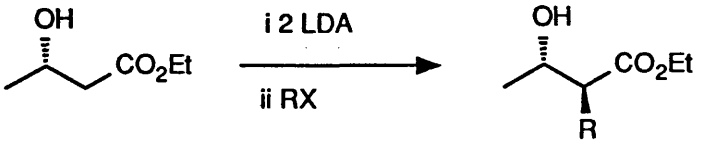

O
CO2Et
bakers
yeast
OH
CO2Et
OH
CO2Et
bakers
yeast
O
CO2Et
(60)
(61)
LDA
Br
LDA, MeI
OH
CO2Et
94 : 6
OH
CO2Et
96 : 4
Na2Cr2O7
Na2Cr2O7
O
CO2Et
O
CO2Et
(S) 91% ee
(R) 96% ee

Scheme 31

1.11 CHIRAL β-KETO ESTERS FROM CHIRAL β-HYDROXY ESTERS

Chiral β-hydroxy esters are readily available in enantiomerically pure form from β-keto esters *via* bakers yeast reduction[35] or by asymmetric hydrogenation.[36]

Frater and coworkers have investigated the stereoselective α-alkylation of chiral non-racemic β-hydroxyesters[37] (Scheme 30).



(59)

R = CH_3, allyl, benzyl ; 95:5

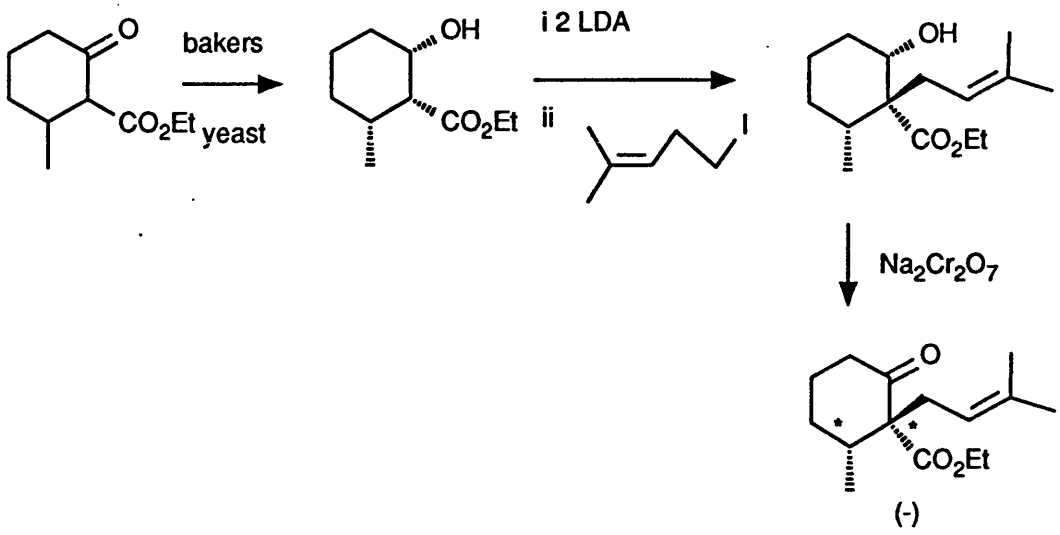
Scheme 30

Generation of a dianion and trapping with an alkylating agent gave a good yield of the adducts **(59)** with a diastereoselectivity of 95:5.

This method has been used to prepare enantiomerically pure β-keto esters of known absolute configuration. (Scheme 31). This procedure has been used by other workers in this area to verify their results.[5,33]

The bakers yeast reduction of ester **(60)** and **(61)** is enantioselective (ratio 3:1), but the stereochemistry at C-2 is of no consequence as it is destroyed in the subsequent deprotonation step to form the dianion.

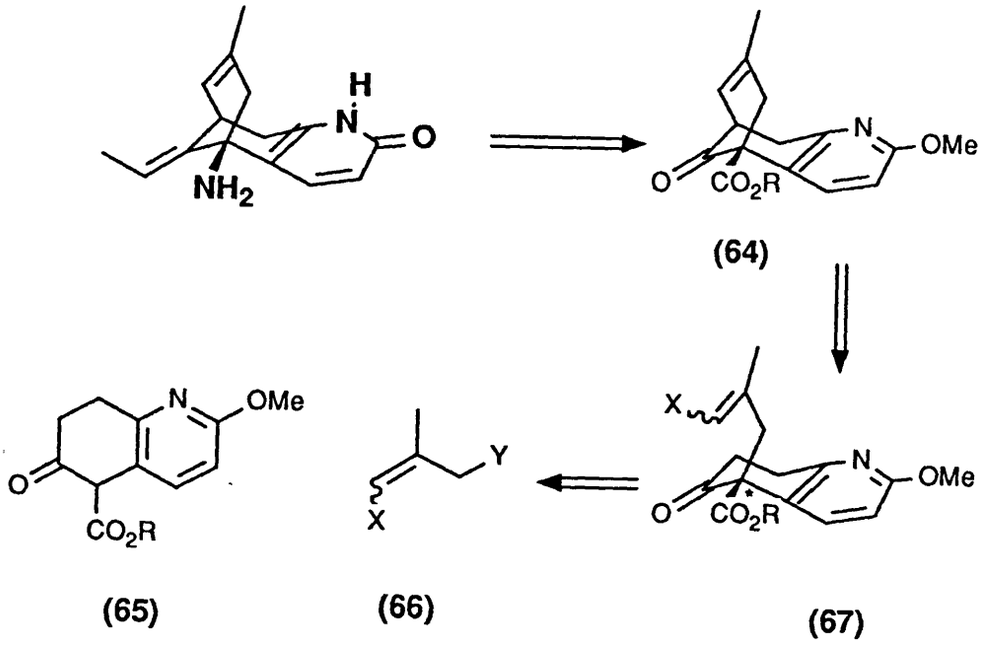
This work has been extended to elaborate two contiguous stereocentres.[38] (Scheme 32).



Scheme 32

The alkylation and oxidation of chiral β-hydroxy esters represents a practical entry to substituted β-keto esters with high enantiomeric purity.

RESULTS AND DISCUSSION

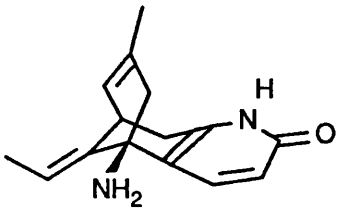


Scheme 33

THE ASYMMETRIC ALKYLATION OF β-KETO ESTERS

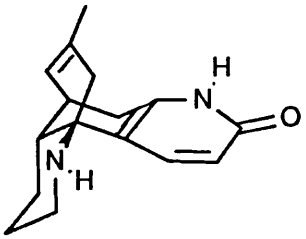
2.1 INTRODUCTION

Huperzine A (**62**) and huperzine B (**63**) are lycopodium alkaloids isolated from a Chinese folk medicine, *Huperzia serrata* and reported in 1986.[39]



huperzine A

(62)



huperzine B

(63)

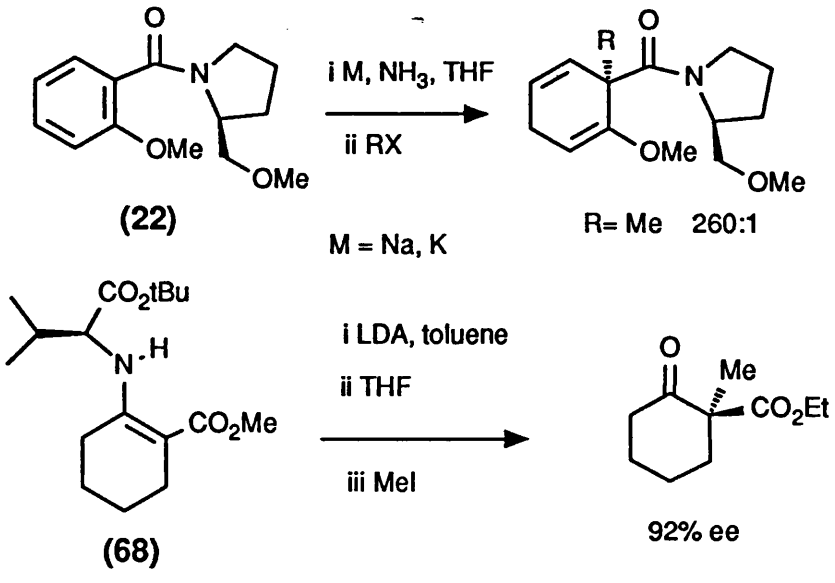
Huperzine A is a potent acetylcholinesterase inhibitor and as such is of interest in the treatment of various forms of memory impairment including Alzheimers disease.[40]

The biological activity and synthetic studies of huperzine A and B will be described in detail in Chapter 5. However, we were interested in the development of an asymmetric synthesis of huperzine A. A retrosynthetic analysis of huperzine A is outlined in Scheme 33.

It was envisaged that huperzine A could be elaborated by simple functional group interconversion from the bridged intermediate (**64**). This was subsequently demonstrated by Kozikowski in a synthesis of (±) huperzine A.[41]

Asymmetric alkylation of β-keto ester (**65**) with a suitable bifunctional electrophile (**66**) would provide the substituted β-keto ester (**67**) containing a group X, (X = Br, SR). It was proposed that an intramolecular vinyl radical cyclisation of a derivative of ester (**67**) would effect ring closure and provide the bridged intermediate (**64**) in optically pure form.

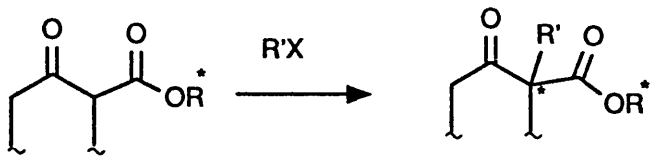
Hence, the key step in an asymmetric synthesis of huperzine A is the asymmetric alkylation of a β-keto ester. A number of approaches to this general problem have been investigated as outlined in Chapter 1. The reductive alkylation of chiral alkoxybenzamide (**22**) developed by Schultz is limited to the synthesis of chiral cyclohexanes.[13] This might be applicable to a synthesis of huperzine A. The more general method of Koga[5] (alkylation of chiral lithioenamines derived from enamine (**68**)) yields substituted β-keto esters with high enantiomeric excess.(Scheme 34)



Scheme 34

Clearly, there is scope to develop alternative solutions to this problem.

Initially, we focused on the alkylation of chiral β-keto esters, where a chiral auxiliary has been incorporated as part of the ester function. (Scheme 35)

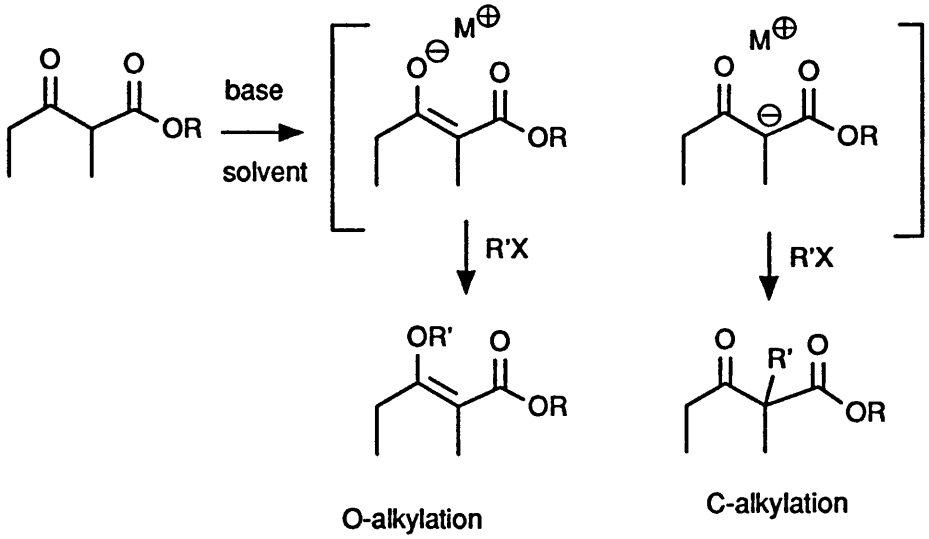


R* = chiral auxiliary

Scheme 35

2.2 β-KETO ESTER ENOLATES AS AMBIDENT ANIONS

The enolates derived from β-keto esters can be described as ambident anions, i.e. they can react at either the carbon or the oxygen site to give two possible products. (Scheme 36)



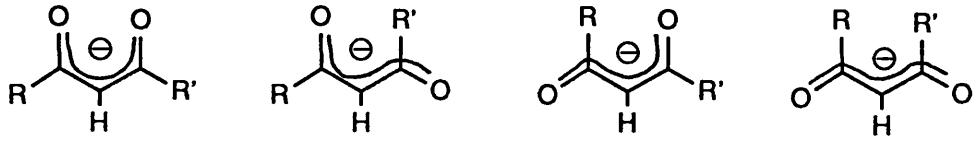
Scheme 36

The ambident reactivity of β-keto ester enolates is influenced by several factors and is not fundamentally understood. The factors influencing the ratio of reaction

at carbon (C-alkylation) or oxygen (O-alkylation) are considered to be the nature of the solvent, the cation, the alkylating agent and the ambident anion itself. The effect of these factors in determining the position of attack on an ambident anion may be considered only for kinetically controlled reactions : in alkylation reactions, the conditions of kinetic control are satisfied in many cases. This area has been reviewed[42] and some general comments can be made.

The chemistry of metal enolates is intimately associated with their structure in solution. It is well known that enolates form aggregates in solution; the structure and reactivity of lithium enolates and the consequences of their complex structures has been reviewed by Seebach.[43]

Additional considerations are necessary with the enolates of β-dicarbonyl compounds.[44] There are four possible conformations of the enolate anion. (Scheme 37)



Possible conformations of anion of $RCOCH_2COR'$

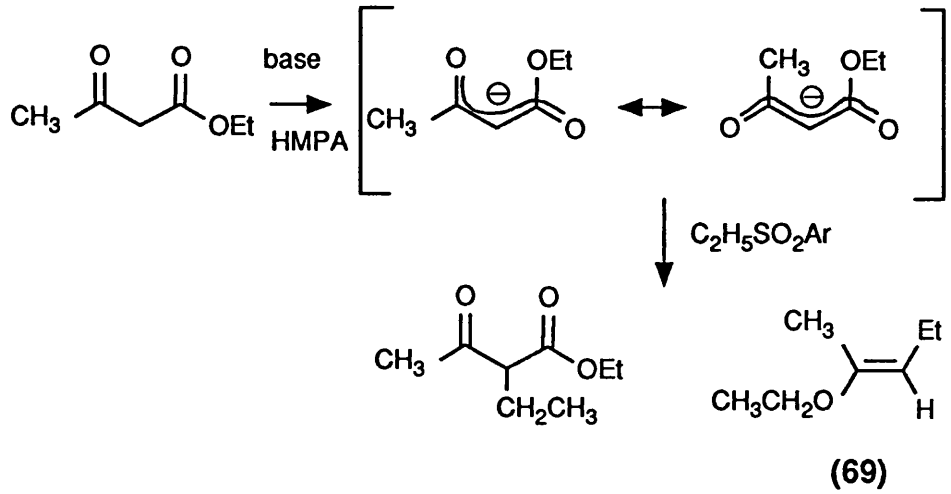
Scheme 37

The enolate can act as a chelating ligand when in the Z,Z conformation which will influence the tendency to form ion pairs. Where all four conformations are possible, in general, they interconvert rapidly as compared with their rate of reaction with electrophiles.

It is possible to draw a number of trends in the ratio of C-alkylated to O-alkylated products (the C:O ratio) in the alkylation of β-dicarbonyl enolates, although the conclusions probably represent an over simplification of the situation.

In estimating the effect of the solvent on the dual reactivity of ambident anion salts, it is necessary to consider two types of solute-solvent interactions; specific solvation of the cation and interaction of the solvent with the anion. In most organic solvents, alkali metal enolates are associated into ion pairs and higher order aggregates and the nature of the solvent determines, to a very large extent, the position of the equilibrium between the species.[44]

In polar, aprotic solvents which can solvate the cation but not the anion (e.g. HMPA, DMSO), it has been established in many cases that alkylation proceeds *via* a free enolate ion. The C:O ratio is essentially independent of the cation. This was demonstrated in the alkylation of the sodium, potassium and caesium enolates of ethyl acetoacetate with ethyl tosylate in HMPA.[45] (Scheme 38)



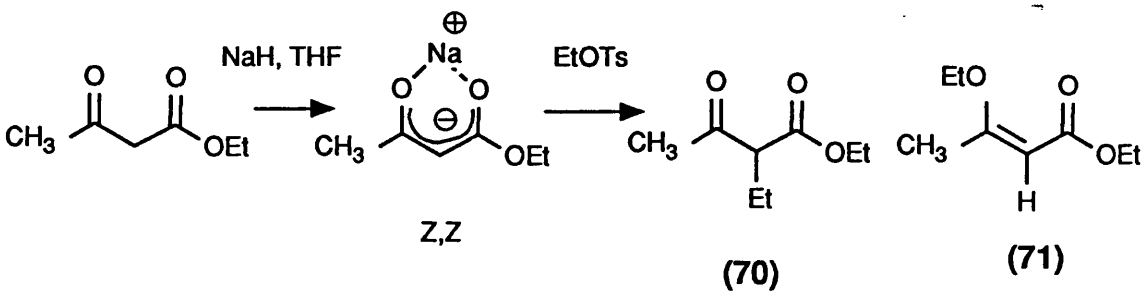
(69)

Scheme 38

The C:O ratio is the same for all the three enolates and, furthermore, only the

trans enol ether (**69**) is formed by O-alkylation. This geometric isomer is derived from the E,E or E,Z conformation of the enolate which is characteristic of the free anion. The Z,Z isomer can only exist as the ion pair as chelation is necessary to offset the destabalising Coulombic interactions between the two oxygen atoms in this conformation. In HMPA, the cation is coordinated by the solvent and hence, is not available, so the anion cannot adopt the Z,Z conformation.

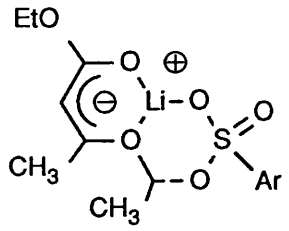
In weakly polar, aprotic solvents which can solvate cations to varying extents (e.g. THF, diethyl ether) the reactive species is apparently an aggregate of some degree.[44] Evidence for an ion pair was obtained in the reaction of the sodium enolate of ethyl acetoacetate with ethyl tosylate in THF. The major product of the reaction (**70**) arises from C-alkylation (90%) but the enol ether (**71**) formed by O-alkylation is the cis-isomer which must arise from the chelated Z,Z conformation of the enolate.[46] (Scheme 39)



Scheme 39

Also, the rate of reaction is much lower in THF than in HMPA which is presumably a consequence of aggregation. In general, the highest C:O ratios for the alkylation of β-dicarbonyl compounds are obtained in these solvents.[44]

Selective solvation of the anion occurs in polar, protic solvents (e.g. water, alcohols) leading to high yields of C-alkylated products.[42] The more



(72)

electronegative oxygen site is solvated by hydrogen bond formation and, hence, is shielded from attack by an external electrophile.

In non-polar solvents which have no coordinating ability (e.g. benzene, alkanes), the ambident anions tend to form micelles which undergo alkylation with the major product arising from C-alkylation.[47]

The role of the cation in influencing the C:O ratio of alkylation of β-dicarbonyl compounds is to some extent dependent on the reaction solvent. However, it is recognised that the reactivity of an ambident anion and, in particular, the rate of O-alkylation is a function of the strength of the interaction between the cation and the anion. The cation is associated with the oxygen site of the anion in both ion pairs and higher order aggregates. This association results in a reduction of nucleophilicity at both carbon and oxygen sites. In general, association of the counterion leads to an increased yield of the C-alkylated product. The use of a non-coordinating cation (e.g. quaternary ammonium ions) will favour O-alkylation.[44] The major exception to this general rule based on the strength of oxygen-metal interaction is found with lithium cations and tosyl or sulphate leaving groups in polar aprotic solvents.[48] The alkylation of the alkali metal enolates of ethyl acetoacetate in DME was investigated. With ethyl iodide or ethyl bromide as the alkylating agent the C:O ratio showed the expected trend, $Li^+ > Na^+ > K^+ > Cs^+ > NBu_4^+$. However, when ethyl tosylate was employed, the C:O ratio observed was $Na^+ > K^+ > Li^+ > Cs^+$. Bram *et al* suggested that the lithium cation may provide 'electrophilic catalysis' for the ionization of the tosylate ion *via* a transition state **(72)** which would favour O-alkylation and lead to the observed cis enol ether.

In considering the influence of the alkylating agent on the regioselectivity of alkylation, it is necessary to take into account simultaneously the electronic and steric effects of the alkyl group and the nature of the leaving group.

It is assumed that the majority of alkylation reactions proceed *via* an S_N2 mechanism. The dependence of the C:O alkylation ratio on the structure of the alkyl group has been studied.[49] It was found that the C:O ratio was sensitive to steric hindrance, with a bulky group in the alkylating agent, alkylation at oxygen is favoured over alkylation at carbon. This provides evidence for the S_N2 mechanism for alkylation.

However, the influence of electronic factors is impossible to evaluate separately from steric effects. Attempts to rationalize the C:O ratio with the structure of the alkylating agent have used the symbiosis effect embodied in Pearson's theory of hard and soft acids and bases (HSAB).[50] In this context, this hypothesis requires that replacement of a 'hard' leaving group will occur more readily with a 'hard' than a 'soft' nucleophile. Hence, O-alkylation would be favoured by alkylating agents, the leaving groups of which correspond to 'hard' bases as the oxygen site is 'harder' than the carbon site. This has been observed; C-alkylation of the enolate of ethyl acetoacetate with various alkylating agents is favoured in the order of leaving groups $OTs^- < SO_4^{2-} < Cl^- < Br^- < I^-$ [48,51,51]. Pearson[50b] has assigned $CH_3- > CH_3CH_2- > (CH_3)_2CH- > (CH_3)_3C-$ as the order of decreasing 'hardness' of alkyl groups but this is not observed experimentally and Reutov and coworkers have suggested that HSAB effects are much less important than steric effects for alkyl groups in S_N2 reactions.[51]

General trends can be drawn to explain the observed regioselectivity of alkylation

of β-keto ester enolates but the interplay between the factors influencing the C:O alkylation ratio is not fundamentally understood.

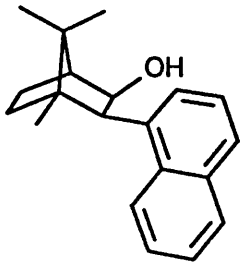
This chapter will describe a study of some alkylation reactions of the enolates of chiral β-keto esters which illustrates the problems associated with ambident anions in alkylation reactions.

2.3 THE PREPARATION OF CHIRAL β-KETO ESTERS

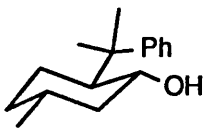
Numerous chiral alcohols have been used as chiral auxiliaries in asymmetric synthesis to achieve high levels of stereocontrol.

Two alcohols were chosen as chiral auxiliaries for investigation; *trans* 2-phenylcyclohexanol **(73)** and the napthylborneol **(49)**. 8-Phenylmenthol **(74)** has been widely used as a chiral auxiliary but its accessibility is hampered by a number of factors[53] and the more readily accessible *trans* 2-phenylcyclohexanol was introduction by Whitesell as an alternative.[54]

(-)-(73)

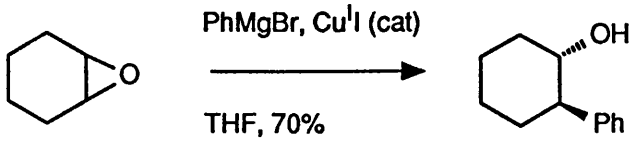


(1R,2R)-(49)



(74)

trans 2-Phenylcyclohexanol is readily prepared in racemic form by copper-catalyzed opening of cyclohexene oxide with phenyl magnesium bromide.[55] (Scheme 40)

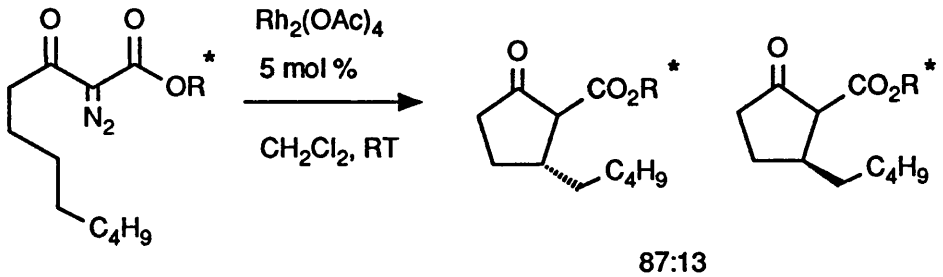


(±) - (73)

Scheme 40

The alcohol **(73)** is available in enantiomerically pure form by enzymatic hydrolysis of the acetates derived from racemic alcohol **(73)**.[54] A small quantity of (1S, 2R)-**(73)** was received as a gift from Hoffman-La Roche. However, in the subsequent reactions, the racemic alcohol was used in order to develop optimal conditions for an asymmetric alkylation reaction before using the enantiomerically pure alcohol.

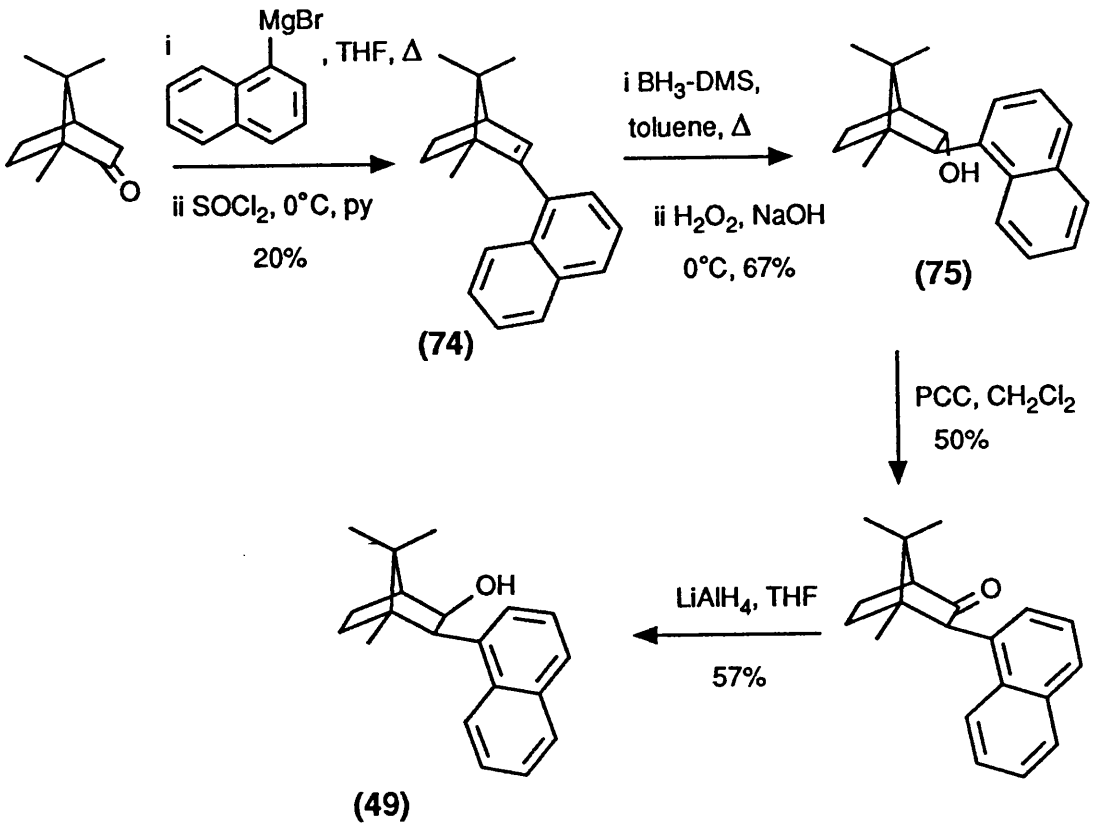
The napthylborneol **(49)** was developed by Taber and used to prepare chiral β-keto esters in a rhodium-mediated intramolecular C-H insertion reaction.[56] (Scheme 41)



87:13

R*OH = **(49)**

Scheme 41


MgBr
i
, THF, Δ
ii SOCl2, 0°C, py
20%
(74)
i BH3-DMS,
toluene, Δ
ii H2O2, NaOH
0°C, 67%
OH
(75)
PCC, CH2Cl2
50%
O
LiAlH4, THF
57%
OH
(49)

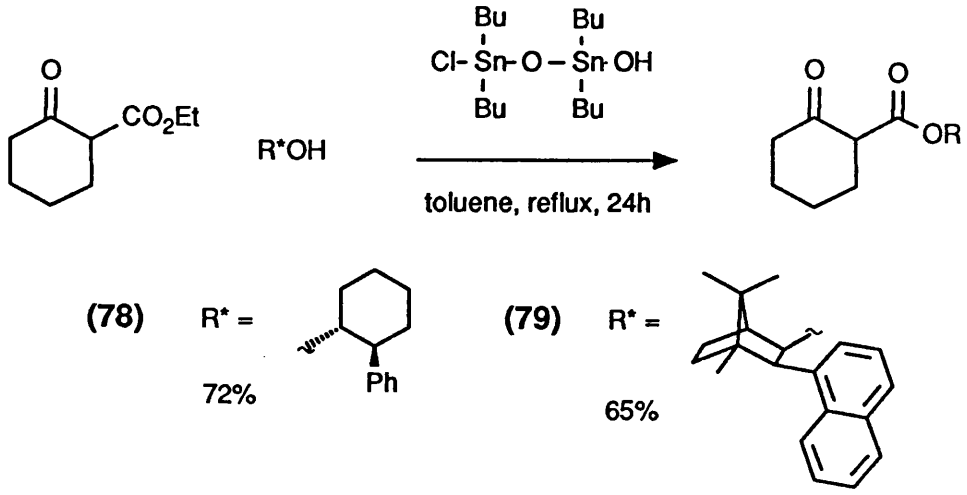
Scheme 42

Napthylborneol (**49**) is prepared from (+)-camphor (Scheme 42)

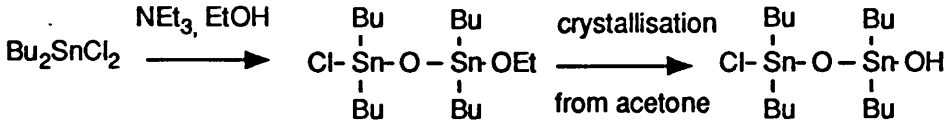
The initial addition of naphthyl magnesium bromide to camphor proved to be a poor reaction. Olefin (**74**) was difficult to obtain free from contamination with camphor and naphthalene when the reaction was attempted on a large scale (0.3 mol). Efforts to improve the yield of this addition by the use of cerium (III) to modify the Grignard reaction were unsuccessful.[57] Addition of the aryl Grignard reagent occurs from the endo face of camphor,[58] but the stereochemistry is destroyed in the subsequent dehydration step to give the olefin (**74**). Hydroboration of this olefin occurs from the less hindered endo face and oxidation yields the *trans* alcohol (**75**). Oxidation with pyridinium chlorochromate gives the ketone which is reduced by lithium aluminium hydride with delivery of hydride from the less hindered face to give the 2-*exo*-hydroxy-3-*exo* naphthylborneol (**49**) in a very moderate 4% overall yield from camphor.

Chiral β-keto esters were prepared by transesterification with the use of a distannoxane catalyst as developed by Otera.[59] This is a very mild method of transesterification which takes place under neutral conditions and has been used by Schreiber to prepare esters that could not be prepared by more conventional coupling methods.[60]

The catalyst (**76**) is prepared from di-*n*-butyltin dichloride. Addition of an ethanolic solution dibutyltin dichloride to a solution of triethylamine in ethanol results in formation of a solid which on crystallisation from aqueous acetone yields the catalyst (**76**).[61] (Scheme 43)


Bu
Bu
Cl-Sn-O-Sn-OH
Bu
Bu
O
CO2Et
R*OH
toluene, reflux, 24h
O
O
OR
(78)
R* =
Ph
72%
(79)
R* =
65%

Scheme 44



(76)

Scheme 43

Refluxing a toluene solution of ethyl 2-oxocyclohexanecarboxylate (**77**) (5 equiv) and the chiral alcohol (**49** or **73**) (1 equiv) with 10 mol% of 1-chloro-3-hydroxy tetrabutylstannoxane (**76**) for 24h gave the chiral esters (**78**) and (**79**) in a moderate yield after distillation to remove excess β-keto ester (**77**) and chromatography. (Scheme 44)

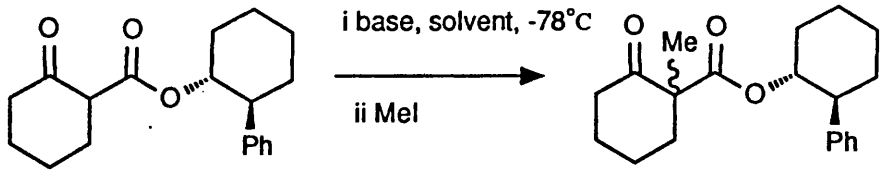
2.4 ALKYLATION OF β-KETO ESTERS

To investigate the viability of our strategy of asymmetric alkylation *via* chiral β-keto esters (Scheme 35), some alkylation reactions of esters (**78**) and (**79**) were studied.

Initially, the β-keto ester (**78**) incorporating racemic alcohol (**73**) was used as the substrate for the alkylation reactions.

Alkylation under thermodynamic conditions, deprotonation with potassium *t*-butoxide in *t*-butanol at 40°C and reaction with an alkyl halide gave the C-alkylated products (**80**) and (**81**) in moderate yield after chromatography. (Scheme 45)

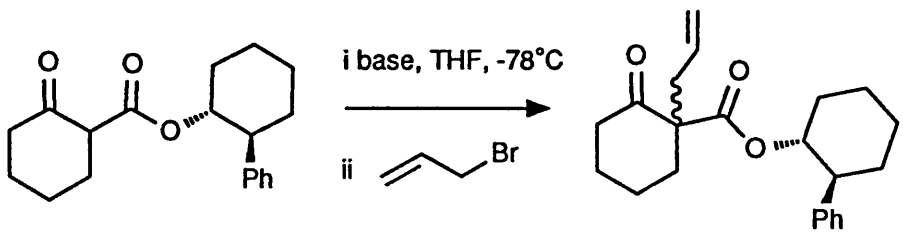
The diastereomeric ratios were obtained from ^{1}H nmr spectra. The ^{1}H nmr spectrum of α-methylester (**80**) shows the two diastereomeric methyl singlets (δ_H



(78) (80)

LDA/ THF	75%	1:1
NaH/ toluene	35%	1:1

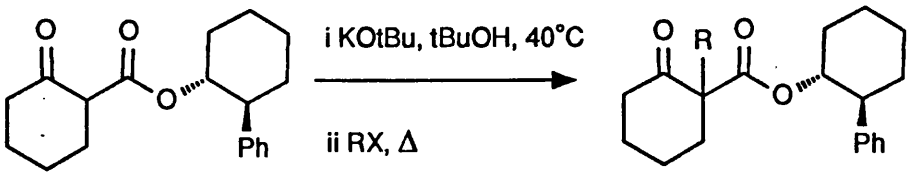
Scheme 46

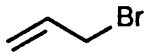


(78) (81)

NaH	65%
KH	50%
LDA	50%

Scheme 47



RX		yield	diastereomeric ratio
MeI	**(80)**	51%	1:1
	**(81)**	67%	-

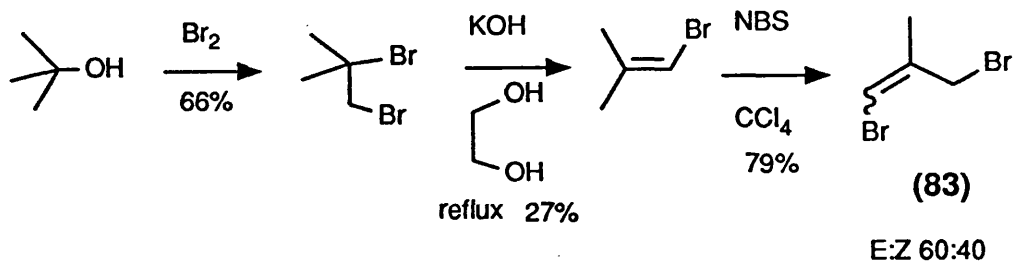
Scheme 45

1.1, 0.8). With the α-allyl ester **(81)** precise determination of the diastereomeric ratio is more difficult as, due to the large number of overlapping multiplets, there is no easily identifiable signal suitable for the determination. However, the diastereomeric ratio appears to be about 1:1.

Alkylation under kinetic control, deprotonation with lithium diisopropylamide in THF at -78°C and trapping with methyl iodide gave the product **(80)** in good yield but with negligible diastereoselectivity as determined by ^1H nmr [1:1 mixture; δ_H 1.1 (1.5H, s); 0.8 (1.5H, s)].

The sodium enolate of β-keto ester **(78)** was generated at room temperature from sodium hydride in toluene. Addition of methyl iodide at -78°C gave a moderate yield of the product **(80)** but again, with essentially no diastereoselectivity being observed. (Scheme 46)

The reaction of 3-bromopropene with the lithium, sodium or potassium enolate of ester **(78)** gave the product **(81)** in moderate yield after chromatography. (Scheme 47)

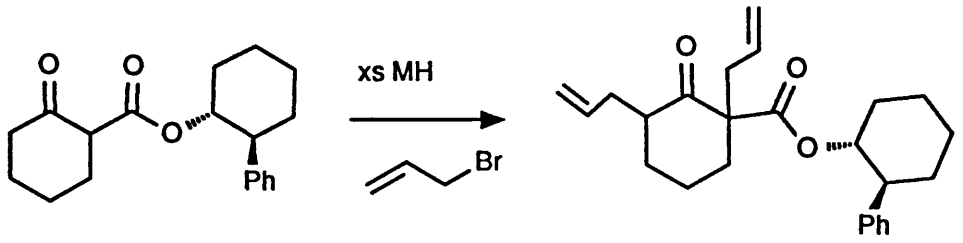


Scheme 49

Again, it was difficult to determine the diastereomeric ratios from the ^{1}H nmr spectrum. Analysis of the ^{13}C nmr spectrum for the reaction of the sodium enolate suggests a ratio of 3:2 as determined from the intensities of the signal of the allylic methylene carbon (δ_C 118.0, 117.7).

A further complication in this reaction arose from the propensity of dialkylation in the presence of any excess of metal hydride base.

Routinely, 1.1 equivalents of base were used in the reaction and it was possible to isolate up to 10% of the dialkylated product (82) by chromatography which was identified by nmr [δ_H 4.7-5.3 (7H, m)] and mass spectral analysis [*m/z* (E.I.), 380, 100%]. (Scheme 48)



(82)

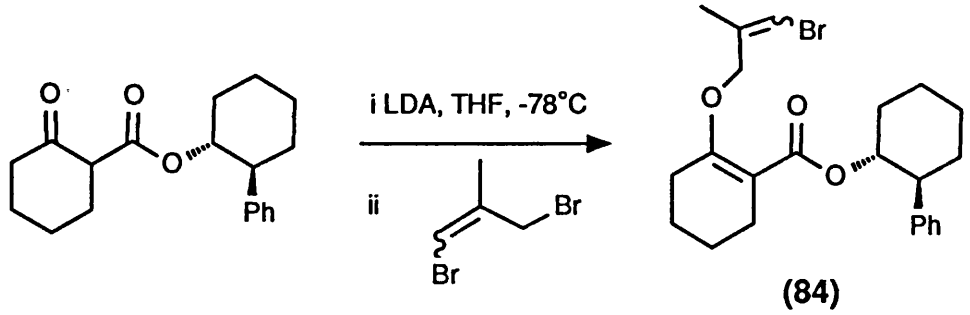
Scheme 48

The levels of diastereoselectivity of reaction of the ester (78) with simple alkyl halides is negligible. Therefore, we wanted to use a more sterically demanding electrophile in the reaction. Considering our longer term goal of synthesis of huperzine A (Scheme 33), 1,3-dibromo-2-methyl-propene was chosen as a suitable electrophile.

1,3-Dibromo-3-methylpropene (83) is prepared by bromination of 1-bromo-2-methylpropene[62] which can be prepared from *t*-butanol.[68](Scheme 49)

The dibromide (83) is formed as a 60:40 mixture of E:Z isomers which are inseparable [δ_H 6.2 (0.6H, brs, = C<u>H</u>Br (E)) and δ_H 6.0 (0.4H, m, = C<u>H</u>Br (Z))]. Hence, the dibromide was used as a mixture in subsequent reactions.

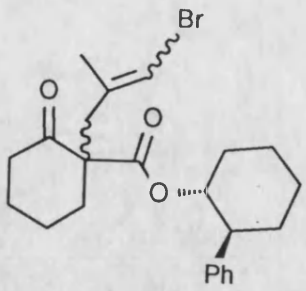
Initial attempts to alkylate the lithium enolate of ester (78) generated with lithium diisopropylamide at -78°C in THF with the dibromide (83) appeared to fail as only starting material (78) was isolated after chromatography. Analysis of the crude reaction mixture by ^{1}H nmr showed that reaction was occurring to give the enol ether (84) arising from alkylation at oxygen. The enol ether was assigned from the ^{1}H nmr spectrum [δ_H 4.1 (1.2H, s) and 4.0 (0.8H, s) E and Z -O-CH_2-]. The enol ether could never be isolated, probably due to its hydrolysis during work up or chromatography. (Scheme 50)



(84)

Scheme 50

A series of alkylation reactions were undertaken to find the conditions needed for C-alkylation. The general procedure for these reactions involved generation of the metal enolate (see Experimental) followed by cooling to -78°C and addition of the electrophile (83). When the reactions were judged to be complete (by TLC), analysis of the crude reaction mixtures by ^{1}H nmr allowed determination of the C:O alkylation ratio [(85):(84)] (Scheme 51). The ratio of diastereomers of the C-alkylated product (85) was determined by integration of the signal of the



(85)

Figure 4: 270MHz ^{1}H nmr spectrum of (85) mixture of diastereomers.

vinyl proton in the ^1H nmr spectrum [δ_H 5.95, 5.85 (E) and 5.42, 5.37 (Z)]. The results are displayed in Table 3, and a typical ^1H nmr spectrum (entry 2, Table 3) is shown in Figure 4.

The highest C:O ratios were observed with sodium enolates (entries 1-3), although significant amounts of enol ester **(84)** were present in all cases. This is a result of the steric bulk of the alkyl group of the dibromide **(83)** and illustrates the sensitivity of the alkylation reaction to steric factors.

The observed trend in C:O ratio with cation is $Na^+ > K^+ > Li^+$ and appears to be independent of solvent over the limited range studied. The trend predicted by the simple model based on the strength of the metal-oxygen interaction in the enolate is $Li^+ > Na^+ > K^+$. However, this anomalous trend has been observed before by Guibe.[48,65] With lithium enolates (entries 4 and 6), the sole product arises from O-alkylation and is independent of the solvent, suggesting that the reactive species are monomeric ion pairs.[65]

When the leaving group of the alkylating agent is tosylate or sulphate, the tendency of lithium enolates towards O-alkylation has been explained as 'electrophilic catalysis' by lithium.[48] However, this result is observed when the leaving group is a halide (Table 3).[65]

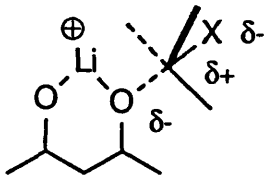
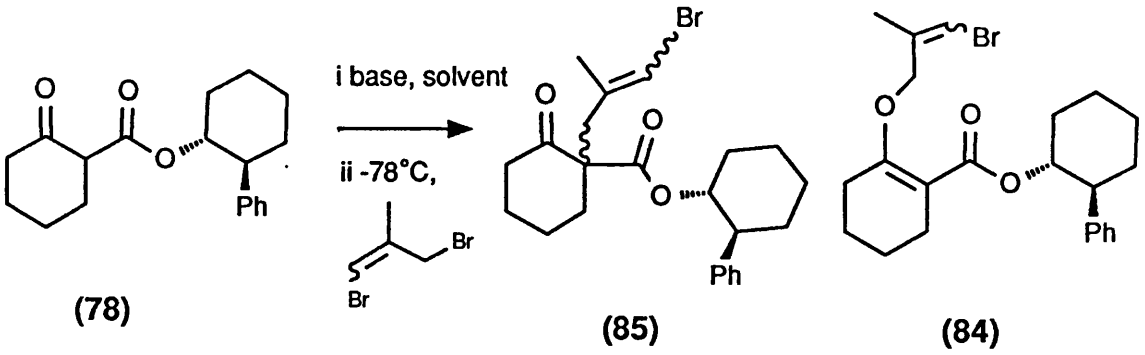


Figure 5

It is assumed that the alkylation reaction proceeds *via* an S_N2 mechanism. A requirement of the S_N2 mechanism is the colinearity of the nucleophile, centre of substitution and leaving group.[66] (Figure 5).It is difficult to envisage an



(78) (85) (84)

Scheme 51

entry	base	solvent	% O-alkylation	% C-alkylation (isolated yield)	diastereomer ratio
1	NaH	THF	20	80 (12)	6:1
2	NaH	DME	20	80 (42)	6:1
3	NaH	DMF	20	80 (14)	6:1
4	LDA	THF	100	0	-
5	LDA	THF/DMPU	-	- (26)	7:1
6	LDA	DME	100	0	-
7	LDA/nBuLi	THF	85	15 (12)	1:1
8	KH	THF	60	40	6:1

Table 3

interaction between the lithium counterion and the halide leaving group, i.e. 'electrophilic catalysis' cannot explain the observation.

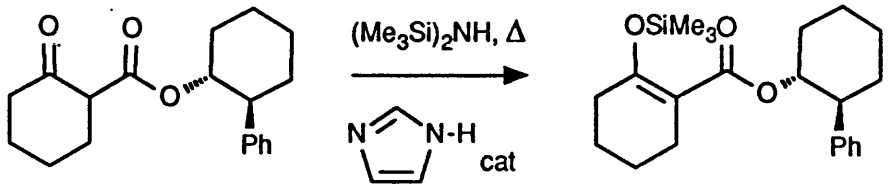
Guibe[65] has suggested that the strong oxygen nucleophilicity of the lithium enolate is a property of the ion pair arising from its chelated structure and independent of the electrophile.

The C-alkylated product (**85**) was obtained from a lithium enolate by addition of a cosolvent, 1,2-dimethyl-2-oxohexahydropyrimidine (DMPU) to the enolate at -78°C,[67] (entry 5, Table 3). The ester (**85**) was isolated in low yield but it was not possible to estimate the extent of O-alkylation due to residual DMPU in the ^{1}H nmr spectrum which obscured the ether signal.

The secondary amine effect has been observed to influence the reactivity of enolates.[43,68] When a lithium enolate is generated using lithium diisopropylamide as a base, diisopropylamine is concomitantly generated. This amine may remain associated with the enolate and influence its reactivity towards external electrophiles. Addition of one equivalent of *n*-butyllithium to the lithium enolate deprotonates this diisopropylamine and frees the enolate from this association. When an equivalent of *n*-butyllithium was added to the lithium enolate of ester (**70**) followed by reaction with dibromide (**83**), 15% of C-alkylated product (**85**) was observed but with negligible diastereoselectivity.

Reaction of the potassium enolate of ester (**78**) with dibromide (**83**) shows a C:O ratio intermediate between Li^+ and Na^+, with O-alkylation slightly predominating. The diastereomeric ratio is 6:1, the same level as observed with the sodium enolate.

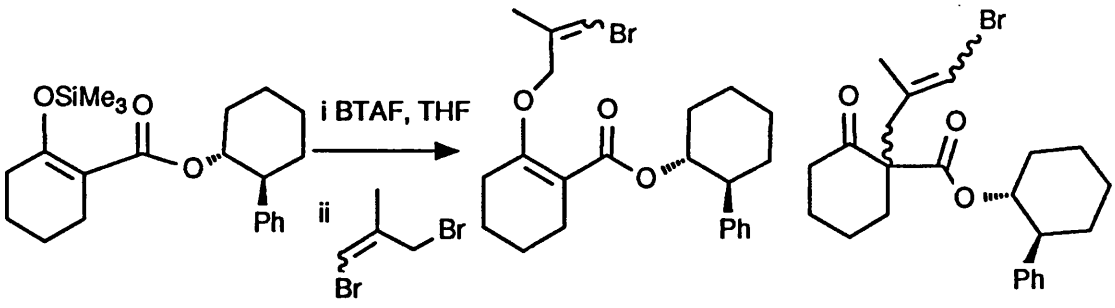
The benzyltrimethylammonium enolate of β-keto ester (78) can be generated from the silyl enol ester (86). Heating the ester (78) with hexamethyldisilazane and a catalytic amount of imidazole gave the silyl enol ether (86) in 74% yield.[69] (Scheme 52)



(78) (86)

Scheme 52

The silyl enol ether (86) was cleaved with benzyltrimethylammonium fluoride to generate the quaternary ammonium enolate[70] which was trapped with dibromide (83). (Scheme 53)



66% 33%, 1:1 diastereomer ratio

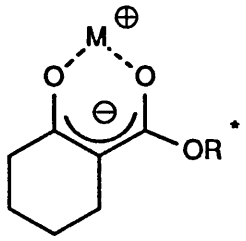
(85)

Scheme 53

The ^1H nmr spectrum of the crude reaction mixture showed a 1:2 mixture of C:O alkylated products with no diastereoselectivity in the α-substituted β-keto ester (85). A high proportion of O-alkylation would be expected with a non-coordinating quaternary ammonium cation which has no ability to reduce the

nucleophilicity of the oxygen site of the anion.

In this limited study of the reaction of enolates of β-keto ester (**78**) and dibromide (**83**), we have shown that the C:O ratio increases in the order $Na^+ > K^+ > NR_4^+ > Li^+$, but is independent of the solvent. The diastereoselectivity of formation of the C-alkylated product (**85**) also varies with cation. The results suggest that the reactive species is an ion pair (**87**).

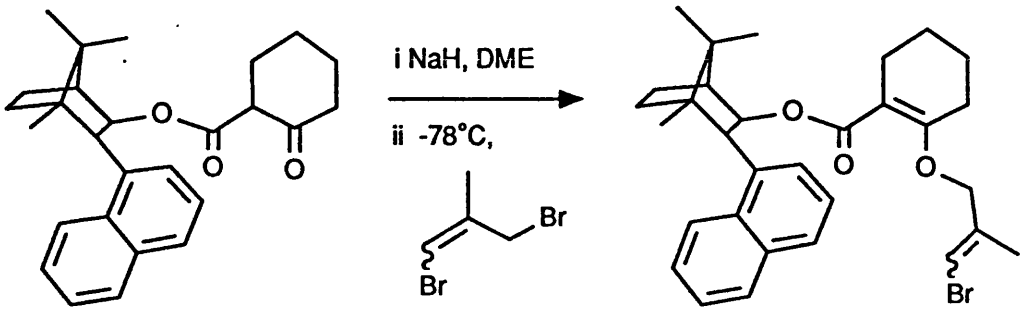


(87)

With the exception of the lithium enolate, the C:O ratio decreases with the chelating ability of the counterion. The role of lithium as a counterion in the alkylation of β-keto ester enolates requires further investigation. The structure of the lithium enolate can be altered by addition of cosolvents or *n*-butyllithium as reflected in the changes in C:O ratio and the diastereoselectivity of alkylation.

Moderate levels of diastereoselectivity were observed in the use of *trans* 2-phenylcyclohexanol as a chiral auxiliary and it was proposed that higher levels of diastereoselectivity would be observed using the more bulky and rigid chiral auxiliary,the naphthylborneol (**49**). The availability of the chiral ester (**79**) was limited by the difficulties associated with the preparation of alcohol (**49**). The enolate was generated using sodium hydride as a base in DME, the optimal conditions for C-alkylation of ester (**78**). After cooling to -78°C, the dibromide was added. Analysis of the crude reaction mixture by ^1H nmr showed the only product to be the enol ester (**80**), the product of O-alkylation. The enol ether was

identified by the appearance of the vinyl protons [δ_H 6.4 (0.6H, s, E) and 6.0 (0.4H, s, Z)] and the protons α to the ether oxygen [δ_H 4.0 (0.8H, s, Z) and 3.9 (1.2H, s, E)]. The product (88) could not be isolated and characterized due to its sensitivity to hydrolysis. (Scheme 54)



(88)

Scheme 54

The increased steric bulk of the naphthylborneol (49) fails to increase the level of diastereoselectivity and simply acts to block alkylation at the carbon site.

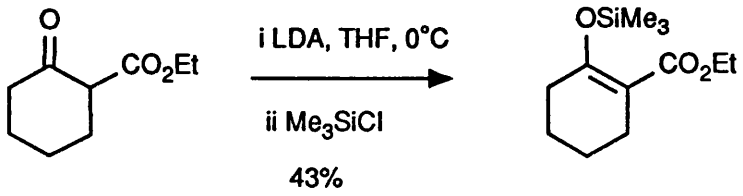
Despite the moderate levels of diastereoselectivity observed using *trans* phenylcyclohexanol as a chiral auxiliary, the severe problems associated with controlling the regioselectivity of alkylation of β-keto ester enolates represents a serious obstacle to the further development of this approach to the asymmetric alkylation of β-keto esters. Hence, this approach was abandoned and alternative systems sought where the problems of O-alkylation were precluded.

2.5 ALKYLATION OF SILYL ENOL ETHERS

The Lewis acid catalysed addition of α-chlorosulphides to silyl enol ethers represents a regiospecific method for the introduction of thioalkyl substituents α to the carbonyl group of enolizable carbonyl compounds.[71,72] However, to our

knowledge, this method had not been applied to β-keto esters.

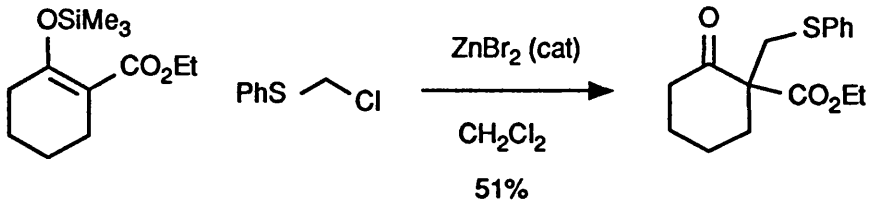
Model reactions were carried out on 1-carbethoxy-2-trimethylsilyloxy-1-cyclohexene (**89**), which was readily prepared from the β-keto ester (**77**).[73] (Scheme 55)



(**77**) (**89**)

Scheme 55

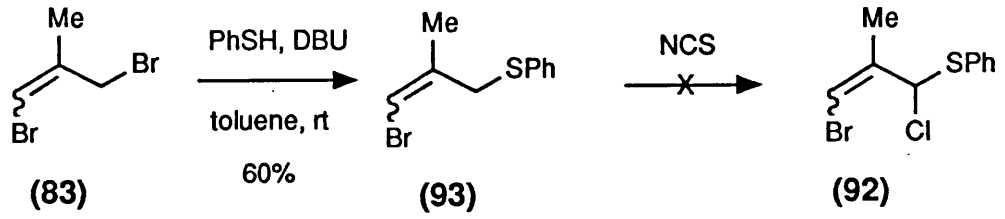
Addition of a catalytic amount of anhydrous zinc bromide to a solution of chloromethylphenyl sulphide and silyl enol ether (**89**) at room temperature in dichloromethane gave the thioalkylated product (**90**) in 51% isolated yield. (Scheme 56)



(**90**)

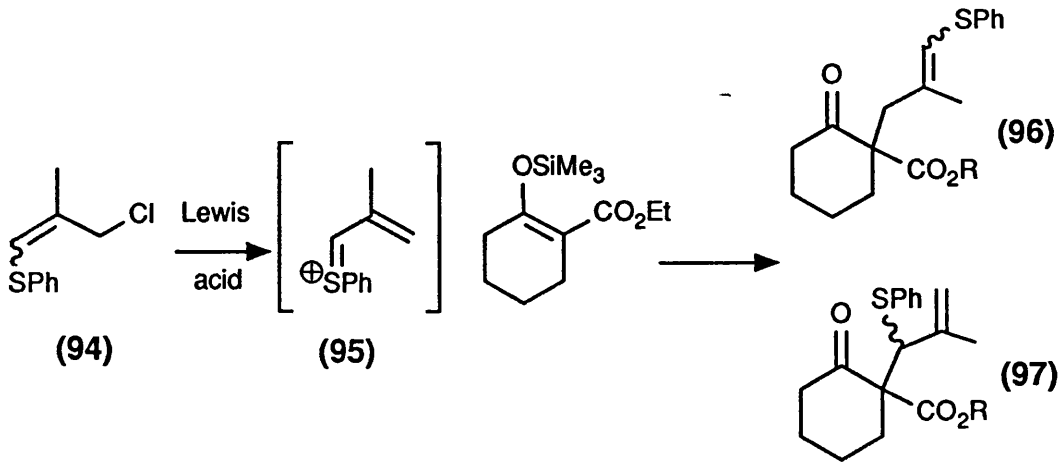
Scheme 56

The bicyclic skeleton of huperzine A (**91**) could be assembled using this methodology with an α-chlorosulphide (**92**) as shown in Scheme 57.



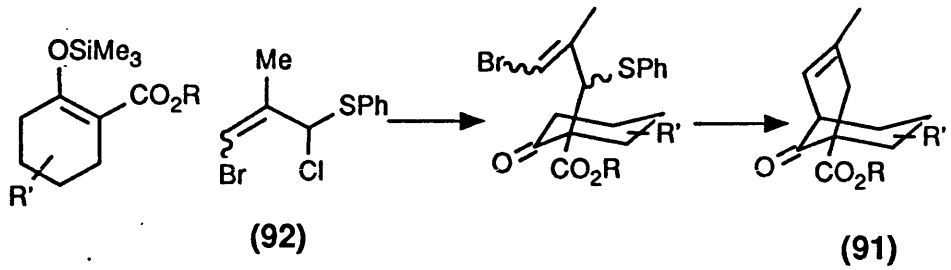
(83) (93) (92)

Scheme 58



(94) (95)

Scheme 59



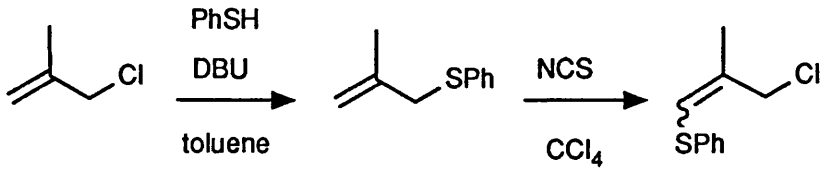
(92) (91)

Scheme 57

The sulphide (**93**) was prepared from the dibromide (**83**) by treatment with thiophenol and DBU in toluene.[74] However, attempts to prepare the α-chlorosulphide (**92**) by chlorination of sulphide (**93**) with N-chlorosuccinimide failed. (Scheme 58)

An alternative strategy involving a γ-chlorosulphide by treatment with a Lewis acid and addition to a silyl enol ether could give two possible products (**96**) and (**97**). (Scheme 59)

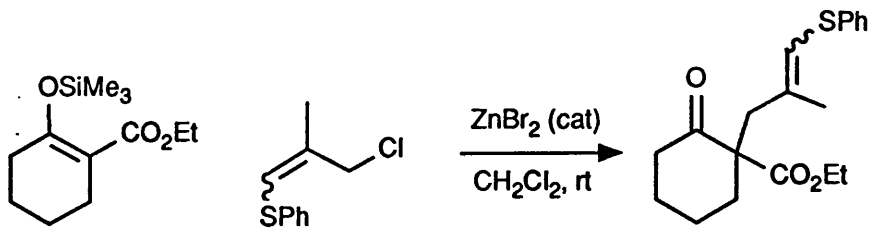
The chlorosulphide (**94**) was prepared (as a mixture of E and Z isomers) by treatment of 3-chloro-2-methylpropene with thiophenol and DBU followed by chlorination with N-chlorosuccinimide.[75] (Scheme 60)



(94)

Scheme 60

When a catalytic amount of zinc bromide was added to a solution of silyl enol ether (**89**) and chlorosulphide (**94**) in dichloromethane, the allylated product (**98**) was isolated in 27% yield. (Scheme 61)

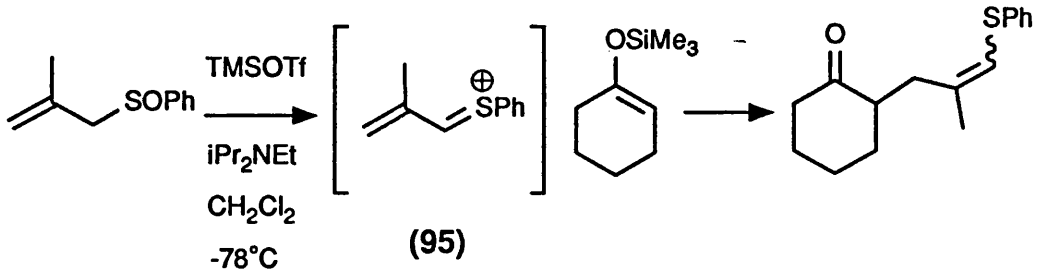


(98)

Scheme 61

The regioselectivity of the reaction was established by ^1H nmr. One vinyl proton is observed [δ_H 6.1 (0.6H, s) and 6.0 (0.4H, s), E and Z isomers].

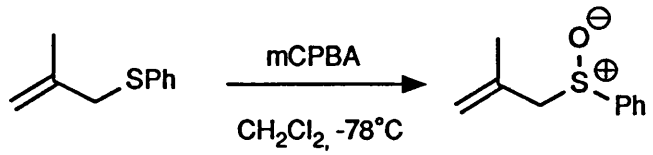
Hunter and Simon[76] had observed the same regioselectivity in the reaction of thionium ion generated from sulphoxides under Pummerer-type conditions with the silyl enol ethers of ketones. (Scheme 62)



(95)

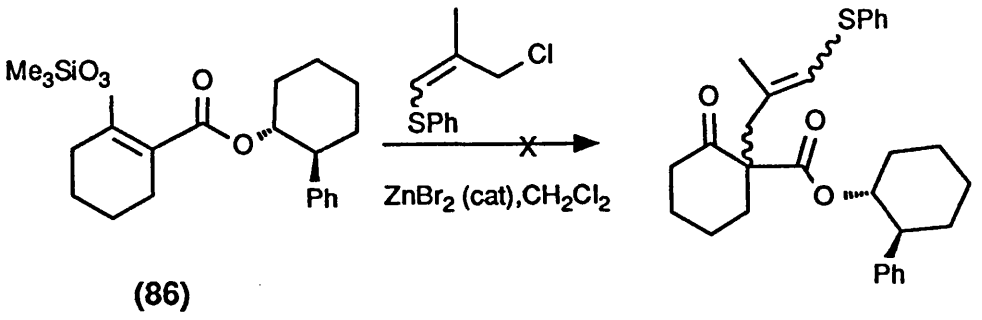
Scheme 62

The sulphoxide (**99**) was prepared by oxidation of the sulphide (**100**) with mCPBA in 90% yield. (Scheme 63)



(100) (99)

Scheme 63



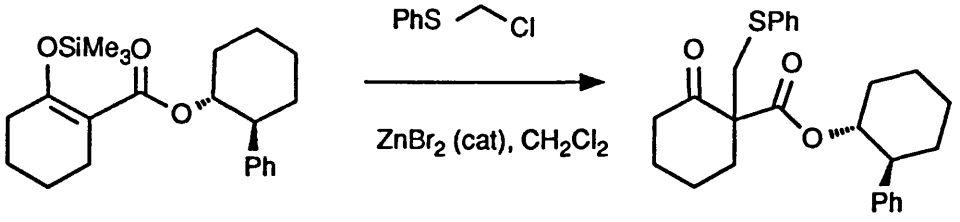
(86)

Scheme 65

Generation of the thionium ion (**95**) from sulphoxide (**99**) using trimethylsilyltriflate and diisopropylethylamine was attempted but on addition of the silyl enol ether (**89**) no alkylated products could be identified.

The successful model reactions were then applied to the silyl enol ether (**86**) incorporating the *trans* 2-phenylcyclohexyl residue as a chiral auxiliary.

Phenylthiomethylation of silyl enol ether (**86**) gave the alkylated product (**101**) in 72% yield as a 3:2 mixture of diastereomers. (Scheme 64)



(86) **(101)**

Scheme 64

The diastereomer ratio was determined by ^{1}H nmr [δ_H 3.22 (0.6H, d, *J* 12.8 Hz); 3.10 (0.6H, d, *J*, 12.8 Hz), and δ_H 2.98 (0.4H, d, *J* 12.8 Hz); 2.83 (0.4H, d, *J* 12.8 Hz)] from the diastereomeric AB quartets of the protons α to sulphur.

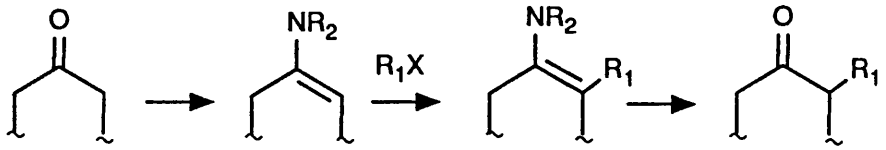
No addition products could be isolated from the reaction of silyl enol ether (**86**) with γ-chlorosulphide (**94**). (Scheme 65)

Phenylthioalkylation of silyl enol ethers of β−keto esters provides a method for selective C-alkylation to give α,α′-disubstitued β-keto esters, overcoming the problems associated with O-alkylation of β-keto ester enolates. However, this approach was not pursued further.

ALKYLATION OF β-KETO ESTER ENAMINES

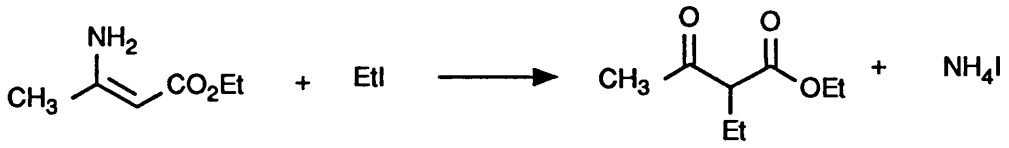
3.1 INTRODUCTION

The alkylation of enamines has long been recognised as a valuable method for controlling alkylation α to a carbonyl group.[77] (Scheme 66)



Scheme 66

As early as 1884, Collie reported the reaction of ethyl iodide with ethyl β-amino crotonate gave, after addition of moist ether, ethyl α-acetyl butyrate and ammonium iodide.[78] (Scheme 67)



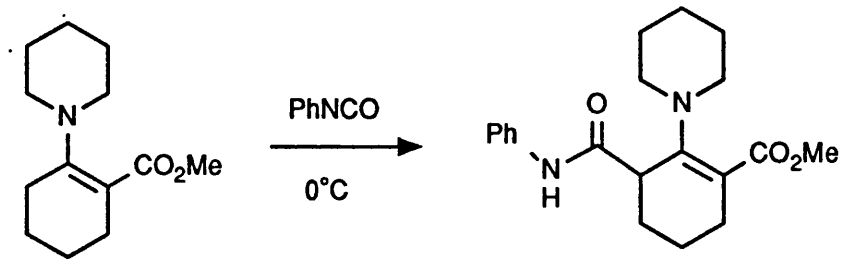
Scheme 67

This method overcomes the problems associated with the alkylation of metal enolates described in Chapter 2; control of regioselectivity (C vs O alkylation), the ease of dialkylation and the potential for self condensation where a strong base is employed, which can lead to dismal results in the attempted alkylation of simple carbonyl compounds.

As part of our investigation into the asymmetric alkylation of β-keto esters, we were seeking a method for the α-alkylation of β-keto esters which precluded the severe problems of O-alkylation of β-keto ester enolates described in Chapter 2.

Hence, we were interested in the potential of alkylation of enamines of β-keto esters as a method for the regioselective alkylation of β-keto esters.

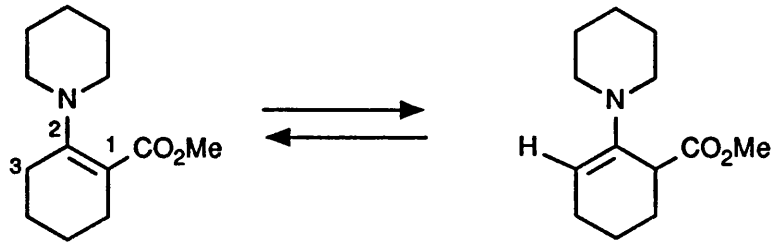
Colonna had reported that the β-enaminoester **(102)** reacted with phenyl isocyanate to give the 1,2,3-substituted cyclohexene **(103)**.[79] (Scheme 68)



(102) **(103)**

Scheme 68

Colonna also observed that the enamines of cyclic β-dicarbonyl compounds exist as an equilibrium mixture of the conjugated **(102a)** and the unconjugated form **(102b)**. For the enamine **(102)** the ratio of conjugated to unconjugated form is approximately 1:1 as determined by integration of the vinyl proton signal in the ^1H spectrum. (Scheme 69)

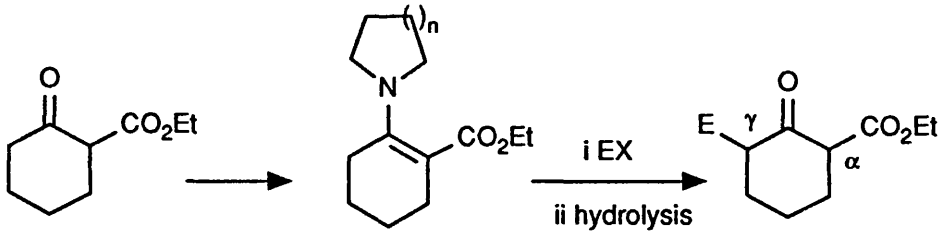


(102a) **(102b)**

conjugated **unconjugated**

Scheme 69

The authors suggested that the reaction with phenyl isocyanate resulted in functionalization at the 3-position due to the greater reactivity of the enamine tautomer **(102b)** over the vinylogous urethane tautomer **(102a)**.



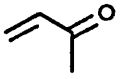
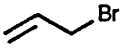
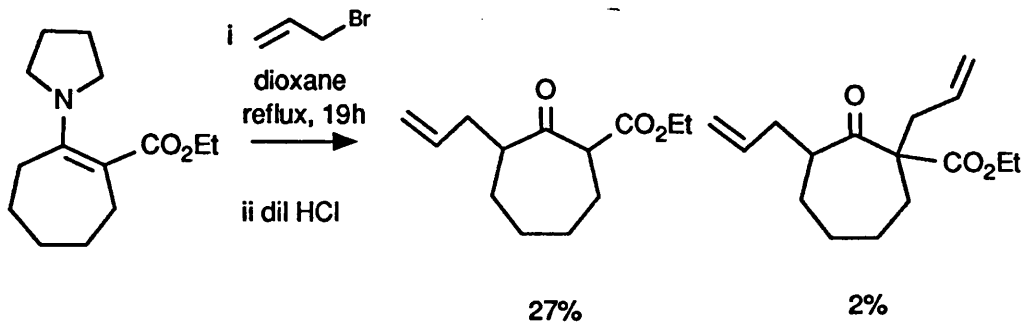
EX	n	t, T	yield
Br_2	2	2h, -95°C	64%
PhSeCl	2	0.5h, 110°C	93%
	2	66h, 101°C	72%
	1	11h, 101°C	75%
	1	97h, 95°C	64%

Table 4

Gravel and Labelle extended this report and investigated the regioselectivity of reaction of cyclic enaminoesters with a range of electrophiles.[80] They found that electrophiles react with enamine derivatives of six membered ring cyclic β-keto esters to give only the 3-substituted products (Table 4), which they called the γ-functionalized β-keto ester.

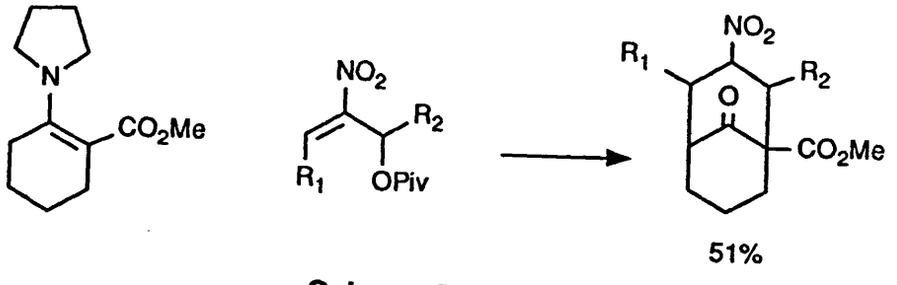
The reaction times are long as compared to unsubstituted enamines but moderate to good yields of product are obtained and can be optimised by correct choice of the amine portion of the enamine.

The enamines of carbethoxycyclopentanone and carbethoxycycloheptanone are not as consistently reactive as the enamines of carbethoxycyclohexanone. Although the γ-alkylated product were favoured, products arising from dialkylation were also observed. (Scheme 70).



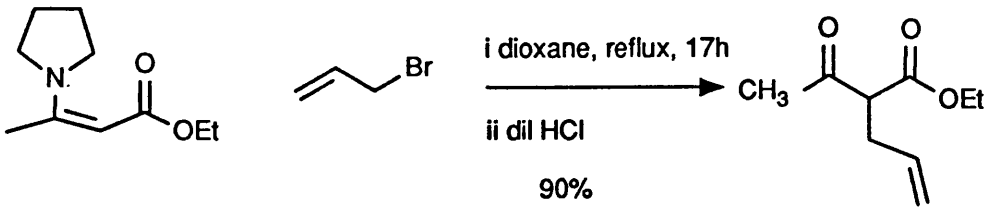
Scheme 70

Gravel and Labelle also noted that the enamines derived from acyclic β-keto esters show differing regioselectivity depending on the electrophile, and this can be illustrated by reaction of the enamine **(104)** and allyl bromide which gave the α-adduct **(61)** in good yield. (Scheme 71).



51%

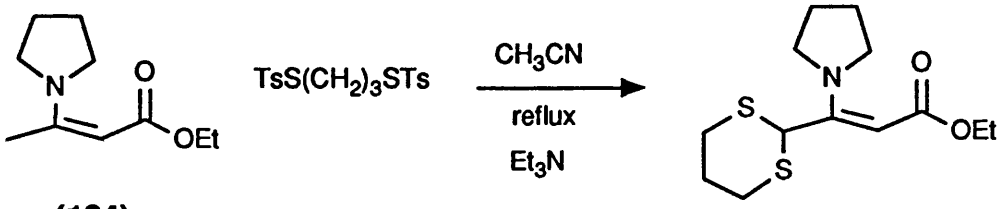
Scheme 74



(104) (61)

Scheme 71

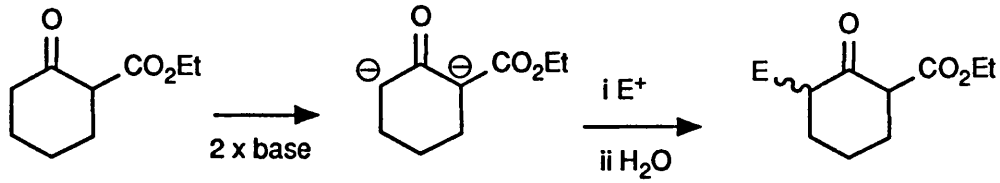
However, under different conditions,[81] the enamine (**104**) was observed to show exclusive γ-reactivity. (Scheme 72).



(104)

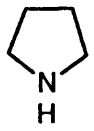
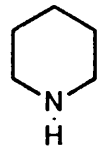
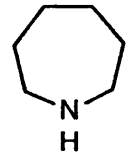
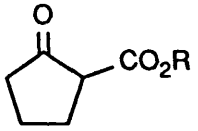
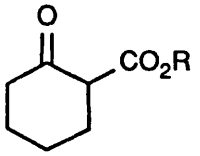
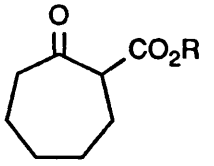
Scheme 72

Alkylation of enamines of β-keto esters in the cyclohexane series provides a mild method for γ-alkylation of β-keto esters and does, as a result, provide an alternative to the dianion method of Huckin and Weiler.[82,83] Although the dianion method allows regioselective γ-alkylation with a range of electrophiles, the use of strong bases in the generation of the dianion limits its generality. (Scheme 73).



Scheme 73

The enamine method has been used by Gravel to control the regioselectivity of Michael reactions of β-keto esters.[84] (Scheme 74).

				
	R =Me	<1%	<5%	
	R = Et	<1%	<5%	<5%
	R = Me	5%	66%	25%
	R = Et	12%	75%	36%
	R = iPr	15%	75%	36%
	R = Et	<5%		

% of Unconjugated Form in β-Keto Ester Enamines

Table 5

Gravel and Labelle also investigated the factors controlling the equilibrium between the "conjugated" and "unconjugated" forms of the enamines of cyclic β-keto ester.[85]

The enamines were prepared from a β-keto ester, an excess of amine and a catalytic amount of p-toluenesulphonic acid in gently refluxing benzene. The percentage of the unconjugated tautomer was determined by integration of the vinylic proton in the ^1H nmr spectrum and the results are presented in Table 5.

The effect of the amine ring size on the tendency to unconjugation shows a trend of 6>7>5. A similar trend is observed with β-keto ester ring size. Gravel and Labelle rationalized the equilibrium ratios of the conjugated and unconjugated forms by invoking three factors.

(1) For maximum conjugation, the enamine must be planar. However, this requirement would introduce a severe steric interaction between the ester group and the hydrogens α to nitrogen. (Figure 6).

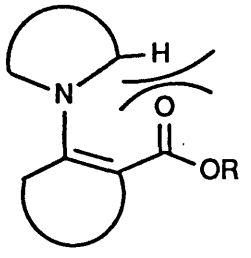
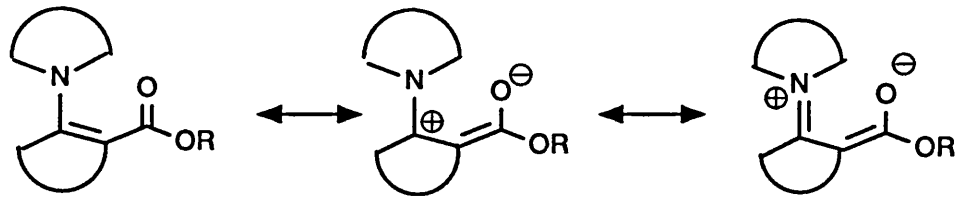


Figure 6

This strain would force at least one of the conjugating groups (the ester carbonyl or the nitrogen lone pair) out of the plane which would lower the resonance energy of the conjugated form. The authors suggested that this steric interaction was not very sensitive to ring size and contributed a similar amount of energy to each enamine. Although this factor can explain the appearance of

the unconjugated form, it does not explain the dramatic differences in equilibrium ratios with ring size as shown in Table 5.

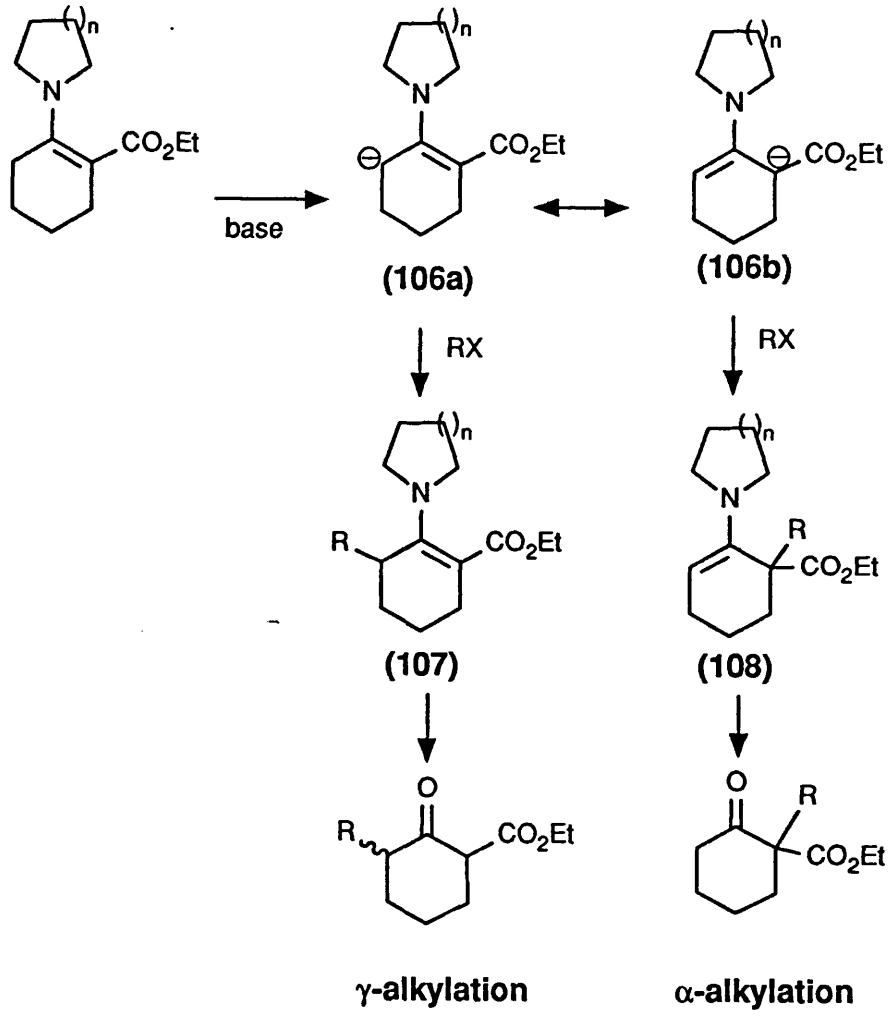
(2) Brown has suggested that the energy difference between endocyclic and exocyclic double bonds varies with ring size.[86] Carbon-carbon double bonds that are exocyclic to five membered rings are favoured over the endocyclic isomer while exocyclic double bonds to six membered rings are disfavoured. Gravel[85] postulated that the relative stability of the resonance hybrid (Scheme 75), was the origin of the observed trends in equilibrium ratio of conjugated to unconjugated enamine with ring size, and that this could be related to the energy differences between endocyclic and exocyclic double bonds.



Scheme 75

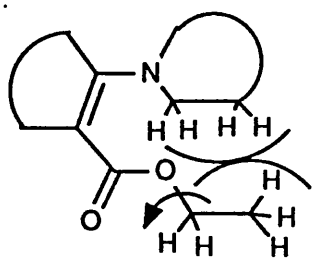
Therefore the conjugated tautomer of the piperidine enamine of cyclohexanonecarboxylate (containing two six membered rings) is most disfavoured as observed (75% unconjugated) whilst the pyrrolidine enamine of cyclopentanonecarboxylate exists in the favoured conjugated form (<1% unconjugated). The observed results imply that the "instability" of exocyclic double bonds to seven membered rings is intermediate between that of five and six membered rings.

(3) The alkyl group of the ester can also influence the equilibrium between conjugated and unconjugated tautomers. Methyl groups shows less tendency to unconjugation than ethyl and isopropyl groups. However, the very similar results obtained with ethyl and isopropyl groups suggests that the inductive

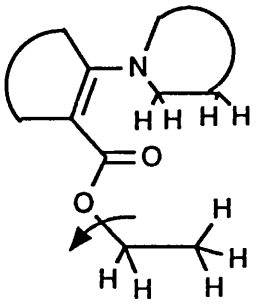


Scheme 76

effect of the alkyl group is not the only factor influencing the equilibrium ratio. Sanchez[87] suggested that extending the alkoxy chain by one carbon results in a loss of rotational freedom in the electronically more stable cis-s-trans conjugation **(105a)** as compared to the cis-s-cis conjugation **(105b)**. Hence, the energy of the tautomer **(105a)** is increased and the equilibrium displaced towards the unconjugated form.



cis - s- trans **(105a)**



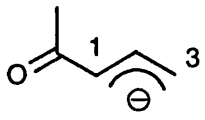
cis- s -cis **(105b)**

As the alkylation of enamines of β-keto esters results in reaction at the γ-position, we decided to investigate the reactivity of the anions of β-keto ester enamines. (Scheme 76).

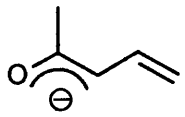
Deprotonation of the enamine gives an allylic anion **(106)** which can potentially react with an electrophile to give either the γ-alkylated product **(107)** or the α-alkylated product **(108)**.

The chemistry of the allylic anions of the enamines of cyclic β-keto esters had not been examined, previous to this work. The chemistry of heteroatom substituted allylic carbanions has been reviewed,[88] and the factors influencing the regioselectivity of reaction are not understood. Gompper has applied the concept of allopolarization to the regioselectivity of reaction of allylic anions,[89] and noted that a 1-acylallylic anion of type **(109)** can also be described as a vinyl substituted enolate ion **(110)**. As the vinyl group is only a weak acceptor,

the anion **(110)** would be expected to display reactions similar to those of an unsubstituted enolate ion, i.e. mainly C-alkylation.



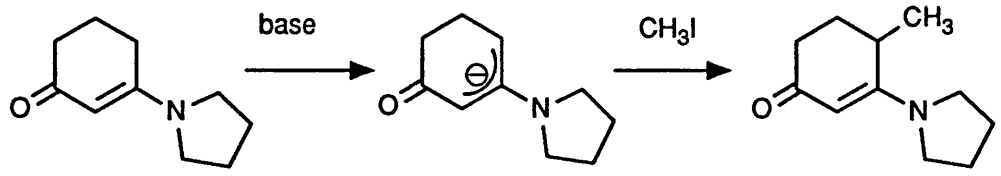
(109)



(110)

Thus, predictions of the regioselectivity of alkylation of allylic anions substituted by both a heteroatom and an acyl group cannot be made with any confidence. The reactivity of some related heteroatom substituted allylic anions has been investigated.

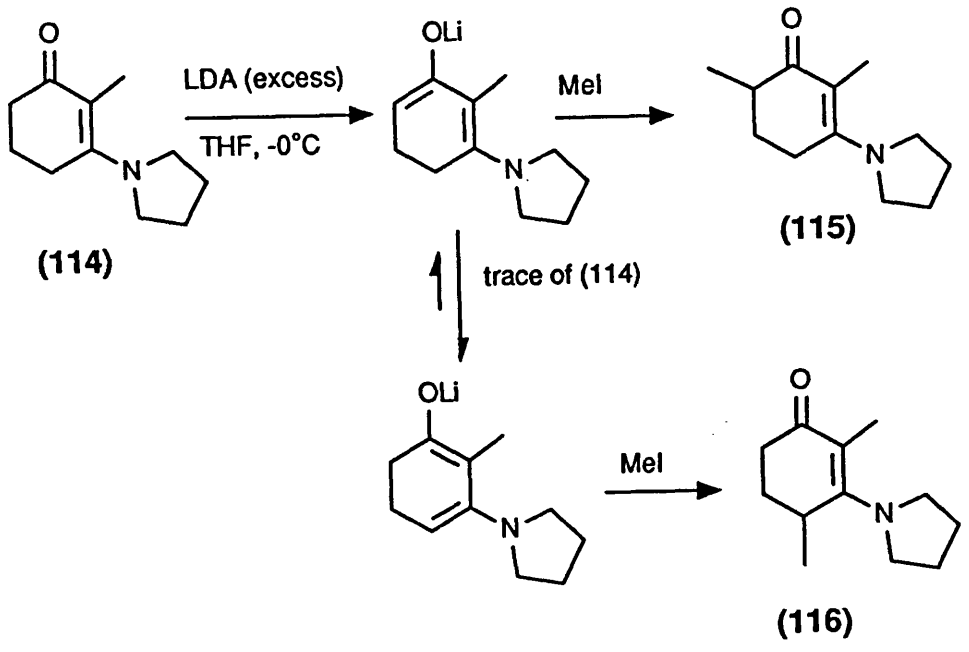
Enaminoketone **(111)** was deprotonated to give the allylic anion **(112)** which is regiospecifically alkylated at the γ-position with alkyl halides.[90,91] (Scheme 77).With n-butyllithium[90] or lithium diisopropylamide[91] as the base, a moderate yield of the γ-alkylated product **(113)** is obtained. An improved yield was observed when potassium hydride was used to generate the allylic anion **(112)**.[92]



(111) **(112)** **(113)**

base	yield
nBuLi	62%
LDA	60%
KH	90%

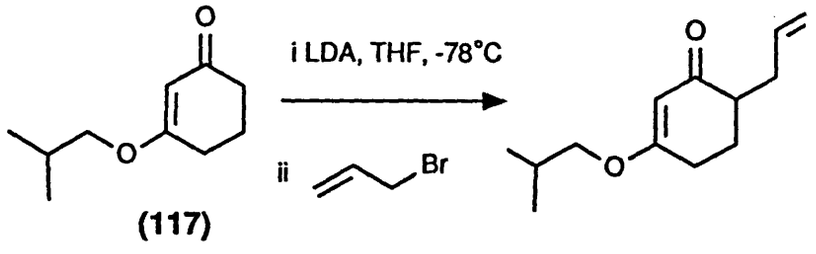
Scheme 77


O
LDA (excess)
THF, -0°C
OLi
MeI
O
N
(114)
(115)
trace of (114)
OLi
MeI
O
N
(116)

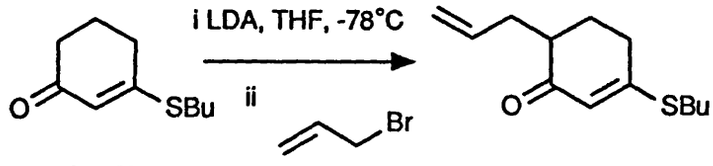
Scheme 78

However, vinylogous amide **(114)** can be alkylated selectively at either the α′ or γ position depending on the reaction conditions.[93] In the presence of an excess of lithium diisopropylamide, the kinetically formed enolate reacts with methyl iodide to give the α′-alkylated product **(115)**, whilst in the presence of an excess of enaminone **(114)**, alkylation of the thermodynamic enolate gives the γ-alkylated product **(116)**. (Scheme 78).

The vinylogous ester[94] **(117)** and vinylogous thioester[95] **(118)** were alkylated at the α′-position *via* the lithium enolate generated with lithium diisopropylamide. (Scheme 79).



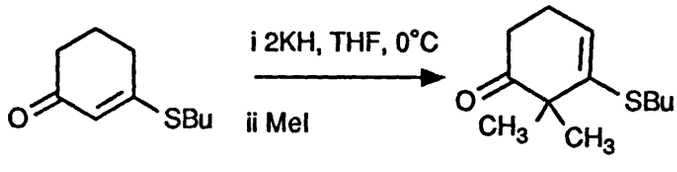
(117)



(118)

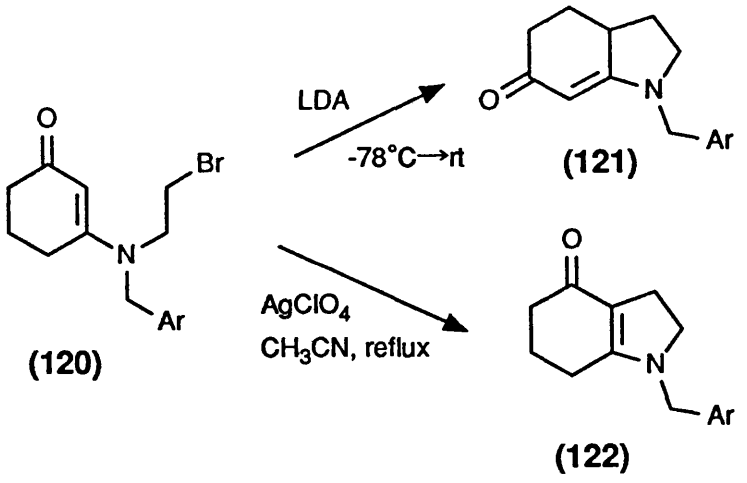
Scheme 79

However, reaction of the thioester **(118)** with potassium hydride (2 equiv) and methyl iodide yielded the α,α-dialkylated product **(119)**.[92] (Scheme 80).



(118) **(119)**

Scheme 80

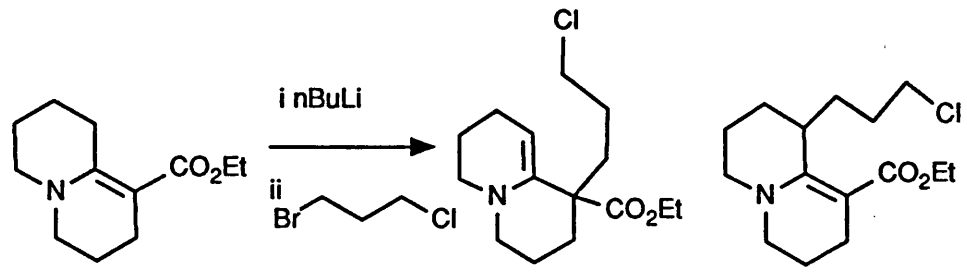


Scheme 81

The regioselectivity of alkylation of the anion of vinylogous amides, esters and thioesters is subject to a number of factors which are not well understood, and in addition, equilibration of the anions leading to thermodynamic control is possible. This equilibration is precluded in the reaction of anions of cyclic β-keto esters.

α-Alkylation has been observed in two isolated examples. Deprotonation of the enamine **(120)** with lithium diisopropylamide results in alkylation at the γ-position to give the product **(121)** and treatment of enamine **(120)** with silver perchlorate in refluxing acetonitrile effected alkylation at the α-position to give the product **(122)**. [96] (Scheme 81).

Treatment of the enamine **(123)** with n-butyllithium in THF and 1-bromo-3-chloropropane gave a 7:1 mixture of α:γ-alkylated products **(124)** and **(125)**.[97] (Scheme 82).

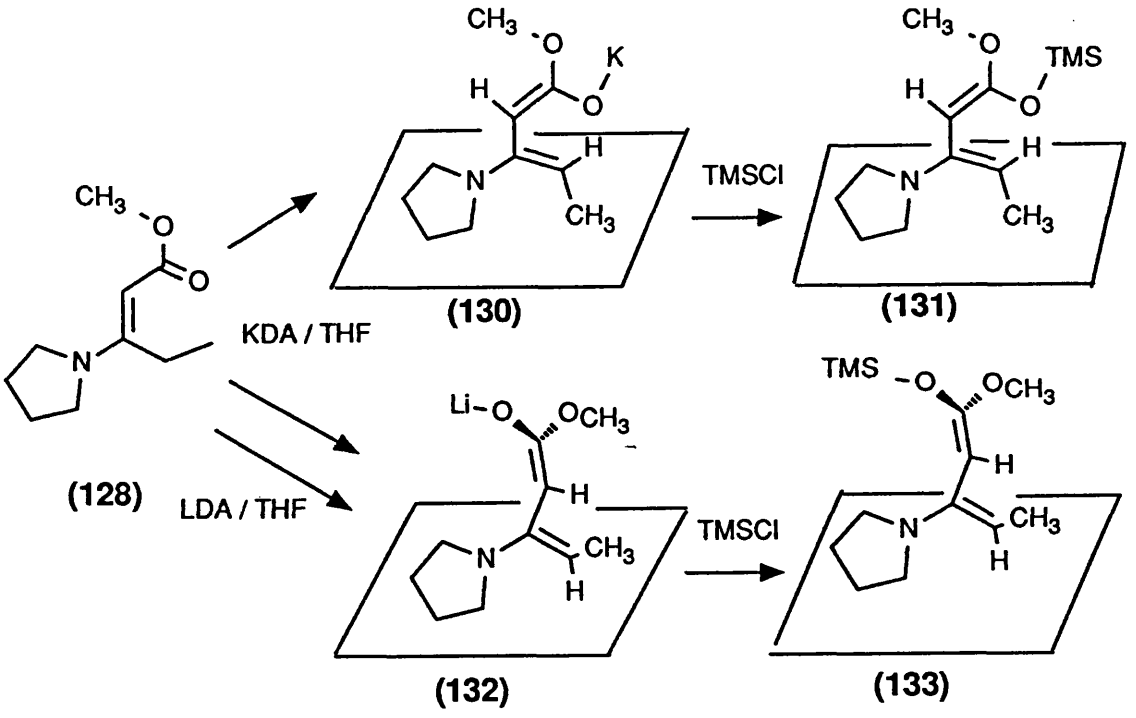


(123) **(124)** **(125)**

Scheme 82

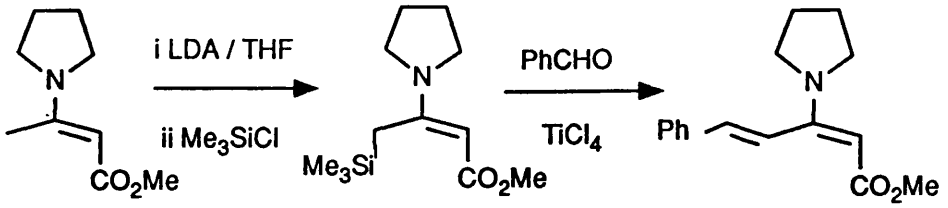
The reactivity of the anions of acyclic enamino esters has been investigated, primarily by Schlessinger.

Kang and Chan found that the anion of enamine **(126)** reacted with chlorotrimethylsilane at the γ-position to give the allylsilane **(127)** which undergoes reaction with carbon-based electrophiles at the γ-position rather than


CH3
O
K
H
O
H
N
CH3
(130)
TMSCl
CH3
O
TMS
H
O
H
N
CH3
(131)
CH3
O
O
KDA / THF
N
(128)
LDA / THF
Li-O
OCH3
H
N
CH3
H
(132)
TMSCl
TMS
O
OCH3
H
N
CH3
H
(133)

Scheme 85

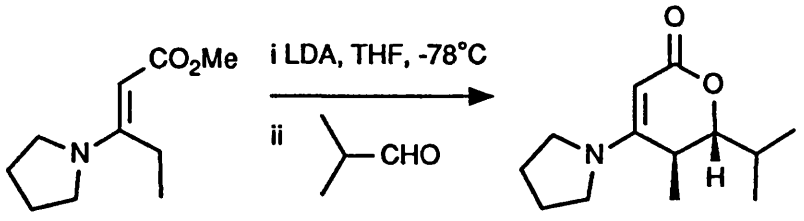
the α-position as might be expected.[98] (Scheme 83).



(126) **(127)**

Scheme 83

Schlessinger observed that the lithium enolate of enamine **(128)** reacted with isobutyraldehyde to give a single lactone product **(129)** *via* an anti-selective aldol reaction at the γ-position.[99] (Scheme 84).



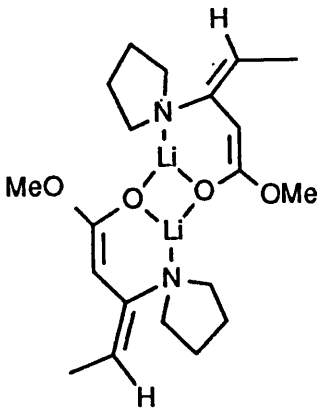
(128) **(129)**

Scheme 84

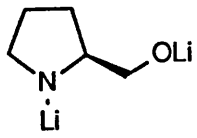
A thorough study of this reaction was undertaken in order to understand the origin of the stereoselectivity of the reaction.[100]

Deprotonation of the enamine **(128)** with lithium diisopropylamide at -78°C and trapping with chlorotrimethylsilane gave a single silyl enol ether **(133)**. Deprotonation with potassium diisopropylamide resulted in a 1:1 mixture of silyl enol ethers **(131)** and **(133)**. (Scheme 85).

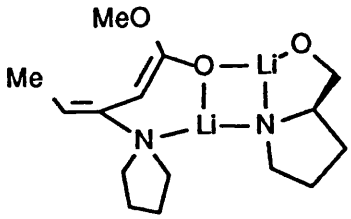
Schlessinger suggested that a twisted diene structure must be present in the enol ether **(133)** and in its enolate precursor **(132)**, as compared to the planar diene structure of the silyl enol ether **(131)** and enolate **(130)**. ^{13}C nmr studies



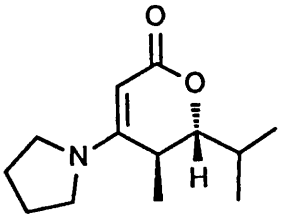
(132)



(136)



(137)



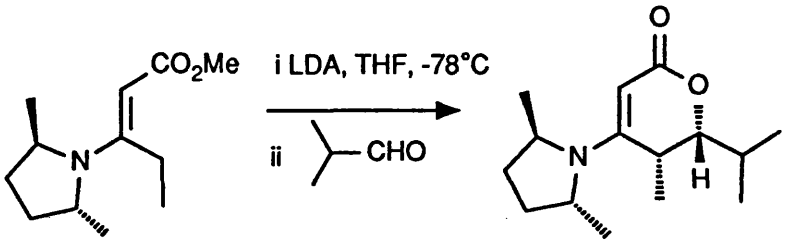
80% de

(129)

Scheme 87

confirmed the twisted diene structure of the enolate **(132)**.

The enantioselectivity available in this reaction was also investigated using the enamine **(134)** where (-)-2,5-dimethylpyrrolidine has been incorporated into the enamine.[101] The lithium enolate of the enamine **(134)** reacts with isobutyraldehyde to give a single syn lactone **(135)** *via* a syn selective aldol reaction with 93% diastereomeric excess. (Scheme 86).

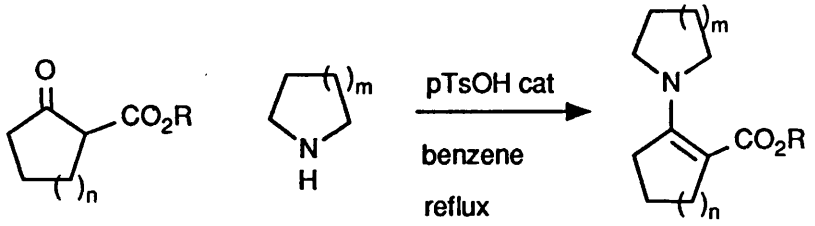


(134) **(135)**

Scheme 86

Schlessinger has speculated on the origin of selectivity observed in this reaction.[102] He has suggested that the reactive species is an enolate dimer and evidence for this was obtained when a 1:1 mixture of the enolates of pyrrolidine enamine **(128)** and dimethylpyrrolidine enamine **(134)** were reacted with isobutyraldehyude. The product lactone was formed with 33% ee. This can be explained if the reactive species are dimers; mixed dimers of the enolate of **(128)** and **(134)** contain the 'achiral' enolate of **(128)** in a chiral environment and an enantioselective anti aldol reaction occurs.

When prolinol is used as the amine portion of the enamine, the lactone **(129)** is formed with 85% ee but this results from an anti selective aldol reaction. These two results have allowed progress towards a second generation catalytic process. When lithioprolinol **(136)** was added to the pyrrolidine enamine enolate **(132)**, the anti selective product **(129)** was obtained in 80% de. (Scheme 87). The mixed aggregate **(137)** must be formed to allow asymmetric induction



(138)

n = 1, m = 1,2,3, R = Et

n = 2, m = 1,2,3, R= Et

n = 3, m = 1, R = Me

Scheme 89

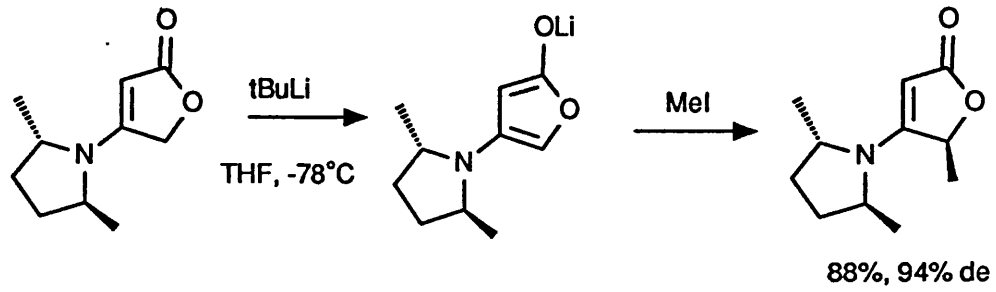
β-keto ester ring size	amine ring size		
	5	6	7
5	2h	16h	4h
6	4.5h	125h	47h
7	27h	very long	very long

Time required for formation of enamine (138)

Table 6

in the aldol reaction. This result represents an exciting step forward.

Finally, diastereoselective alkylation of vinylogous urethanes derived from simple tetronic acids have been investigated and again, exclusive reaction at the γ-position was observed with high diastereoselectivity.[102] (Scheme 88).

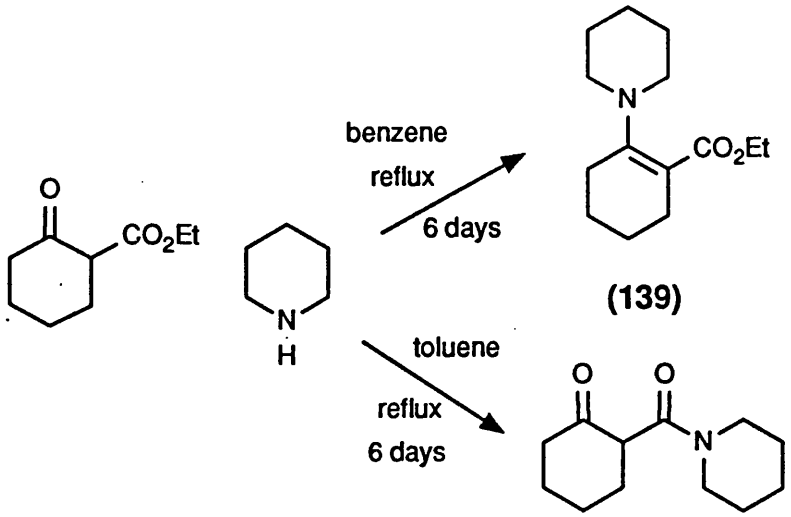


Scheme 88

3.2 PREPARATION OF ENAMINES OF CYCLIC β-KETO ESTERS

A series of β-keto ester enamines **(138)** to be used in this work were prepared using the method of Gravel and Labelle.[80] The β-keto ester, five equivalents of amine and a catalytic amount of p-toluenesulphonic acid were heated to reflux in benzene solution with azeotropic distillation of water (Scheme 89) for the time shown in Table 6. The cyclopentane and cyclohexane derived β-keto esters were commercially available, but methyl cycloheptanonecarboxylate was prepared by carbomethoxylation of cycloheptanone.[104] The piperidine and hexahydroazepine enamines of cycloheptanone carboxylate cannot be prepared by this method as the rate of reaction is too slow.

In the preparation of the piperidine enamine **(139)**, it is imperative to effect the reaction in benzene; substitution with toluene results in the formation of the ketoamide **(140)**. (Scheme 90)



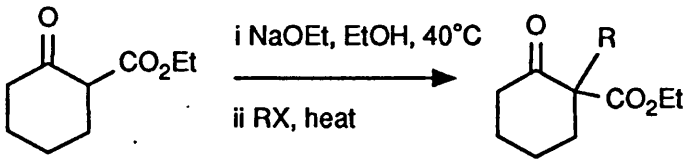
Scheme 90

The ketoamide **(140)** was assigned by the disappearance of the ethyl ester signals in the ^1H nmr spectrum, an amide band in the ir spectrum (1700 cm^{-1}) and from the mass spectrum [*m/z* 209 (M^+)**(140)**].

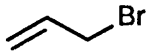
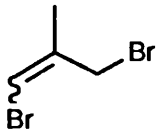
The ratios of conjugated to unconjugated enamines as determined by ^1H nmr using the integration of the vinyl proton of the unconjugated enamines were essentially the same as those of Gravel and Labelle (Table 5).

3.3 ALKYLATION OF THE ANIONS OF CYCLIC β-KETO ESTER ENAMINES

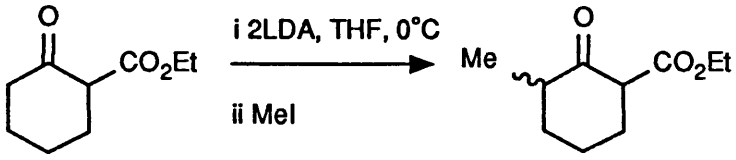
We wanted to investigate the regioselectivity of alkylation of the anions of cyclic β-keto ester enamines (Scheme 76). Initially, we focused on the reactions of ethyl piperidinylcyclohexenone carboxylate **(139)**. This enamine exists predominantly as the unconjugated tautomer (75%), and we were interested to see if the degree of unconjugation of the enamines **(138)**, although a thermodynamic property, was reflected in the reactivity of the kinetic enolates of the enamines. Equilibration of the kinetic and thermodynamic enolates



(77)

RX			
MeI	**(142)**	R = Me	76%
	**(4)**	$R = C_3H_5$	74%
	**(143)**	$R = C_4H_6Br$	70%

Scheme 92

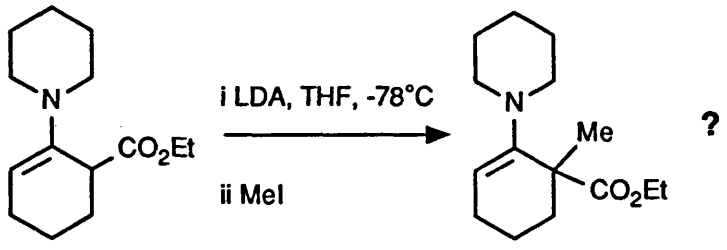


(144)

Scheme 93

observed between the anions of enaminoketones (Scheme 78) is precluded in the anions of cyclic β-keto ester enamines.

The enamine **(139)** was deprotonated using the conditions of Gammill and Bryson.[91] Generation of the lithium enolate using LDA in THF at -78°C followed by trapping with methyl iodide. However, it was difficult to isolate the alkylated enamine **(141)** probably due to its sensitivity towards hydrolysis. (Scheme 91).



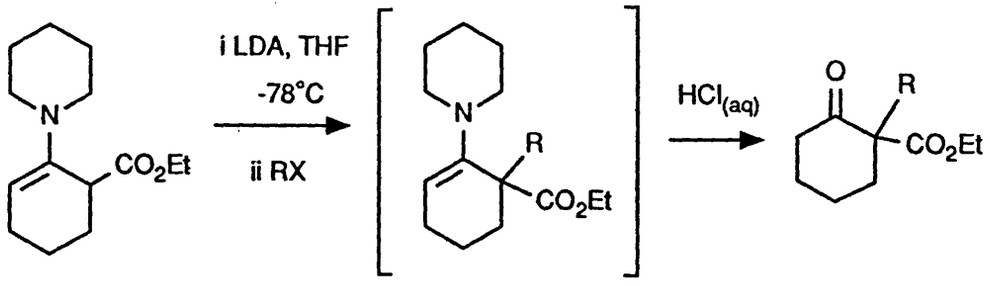
(139) **(141)**

Scheme 91

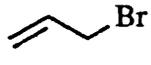
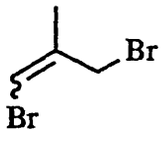
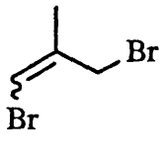
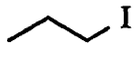
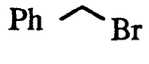
Therefore, in subsequent reactions, the alkylated enamine product was hydrolysed *in situ* by stirring the reaction mixture with 2M hydrochloric acid to release the β-keto ester. The crude reaction mixtures were then analysed by g.c. and ^{1}H nmr and the products were identified by comparison with authentic samples of α and γ-alkylated products prepared by an independent route or by direct comparison with literature data.

The authentic α-substituted β-keto esters **(4)**, **(142)** and **(143)** were prepared under thermodynamic conditions from the β-keto ester **(77)** using sodium ethoxide as the base. (Scheme 92).

Ethyl 3-methyl-2-oxocyclohexanecarboxylate **(144)** was prepared using the dianion methodology of Huckin and Weiler,[52] in 83% yield (Scheme 93). The



(139)

entry	RX		yield	
			nmr	isolated
1	MeI	**(142)**	100%	79%
2		**(4)**	85%	62%
3		**(143)**	26%	20
4	 /DMPU	**(143)**	40%	*
5		**(145)**	40%	*
6		**(146)**	55%	42%

* product not isolated

Table 7

^{1}H nmr spectrum of the γ-alkylated product is complicated by the appearance of both keto- and enol tautomers of **(144)**.

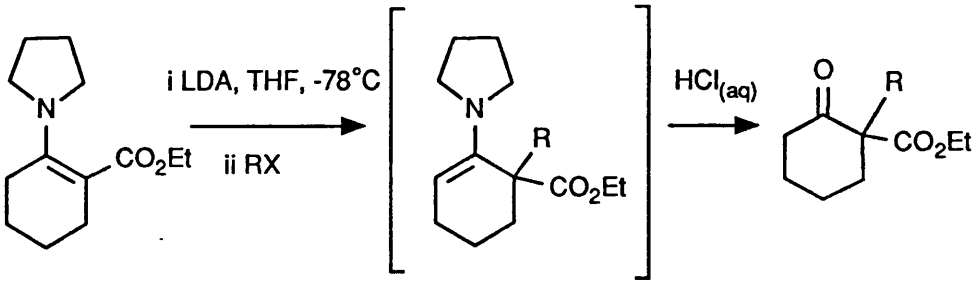
The reaction of the anion derived from enamine **(139)** and LDA with a range of alkyl halides was investigated and the results of this study are shown in Table 7. In all cases, the only product (>95%) observed arose from alkylation at the α-position. Where nmr yields are less than 100%, the remainder of the material was shown by gc and nmr to be the β-keto ester **(77)**. In some cases, the products were isolated and purified by chromatography for complete characterization. No γ-alkylated product was observed in any of the cases studied.

In the reaction with iodomethane (entry 1, Table 7), authentic samples of both α-alkylated product **(142)** and γ-alkylated product **(144)** were available and the absence of the γ-adduct in the crude reaction mixture was demonstrated by gc and ^{1}H nmr.

The products of alkylation with allyl bromide and 1,3-dibromo-2-methylpropene (entries 2 and 3, Table 7) were identified as the α-alkylated products **(4)** and **(143)** respectively by comparison with the authentic samples.

The regioselectivity of alkylation with iodopropane was established to be α by comparison of the ^{1}H nmr spectrum of the product with literature data for the α-alkylated product **(145)**.[105]

Ethyl 1-phenylmethylcyclohexanonecarboxylate **(146)** was identified by the AB quartet of benzylic protons in the ^{1}H nmr spectrum (δ_H 3.81, 1H, d, *J* 14 Hz; 2.86, 1H, d, *J* 14 Hz) which is consistent with alkylation at the α-site, and by



(148)

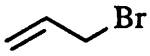
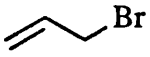
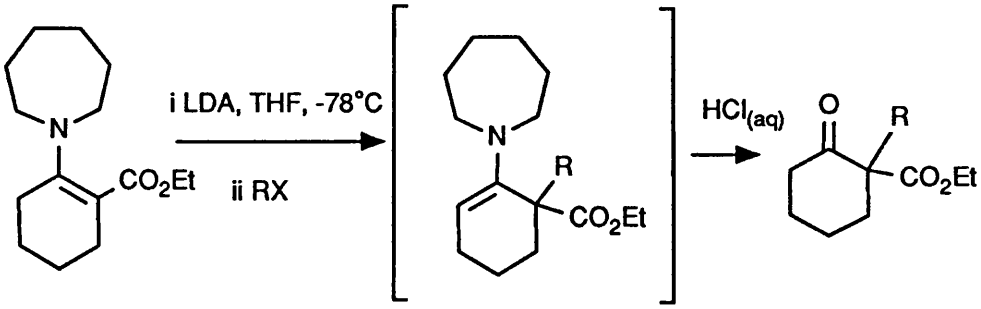
entry	RX		yield (nmr)
1	MeI	**(142)**	80%
2		**(4)**	30%
3	 /DMPU	**(4)**	70%
4	Ph 	**(146)**	0%

Table 8



(149)

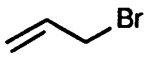
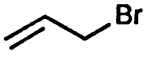
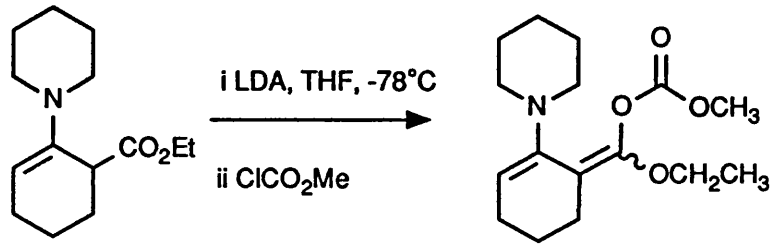
entry	RX		yield (nmr)
1	MeI	**(142)**	60%
2		**(4)**	50%
3	 / DMPU	**(4)**	85%

Table 9

comparison with the literature data for **(146)**[3] and ethyl 3-phenylmethylcyclohexanone carboxylate.[80]

Reaction of the anion of enamine **(139)** with dibromide resulted in a low yield of the product **(143)** (entry 3, Table 7). Addition of DMPU as a cosolvent improved the yield of the reaction to 40% (entry 4, Table 7).

Reaction of the anion of enamine **(139)** with methyl chloroformate appears to yield the carbonate **(147)** arising from alkylation at oxygen (Scheme 94).Before hydrolysis, the crude reaction mixture was shown to comprise a 1:1 mixture of starting material and a product, which was tentatively assigned as the carbonate **(147)** by ^{1}H nmr [vinyl proton, δ_H 5.12, 1H, t, *J* 4 Hz; methyl ester, 3.65, 3H, s], and mass spectral analysis [*m/z* 295 (100%, M^+) **(147)**].

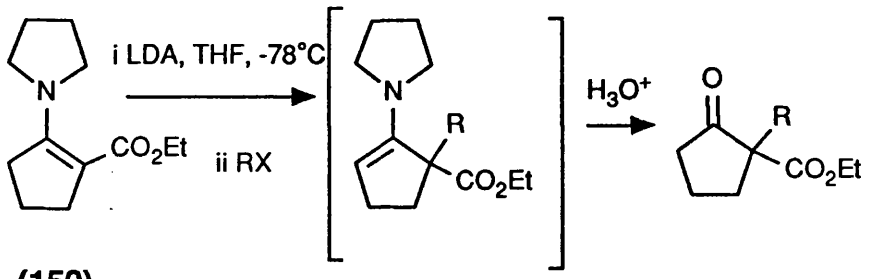


(147)

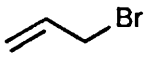
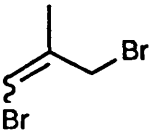
Scheme 94

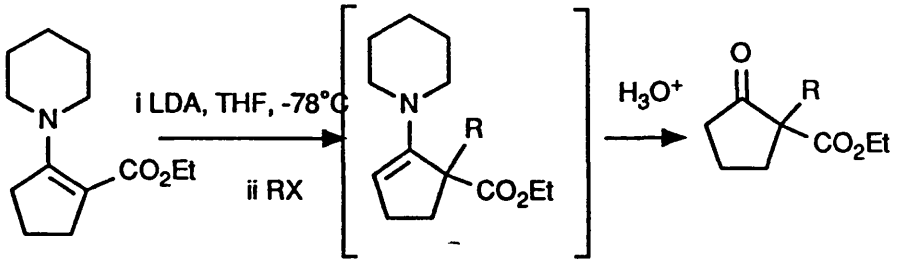
The reaction of the lithium enolates of the pyrrolidine enamine **(148)** and hexahydroazepine enamine **(149)** with alkyl halides was studied and the results are presented in Tables 8 and 9.

Again, the only products observed were the α-alkylated products and when allyl bromide was used as the alkylating agent, addition of DMPU as the cosolvent resulted in an improved yield. (entries 2 and 3, Table 8; entries 2 and 3, Table 9).

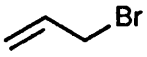


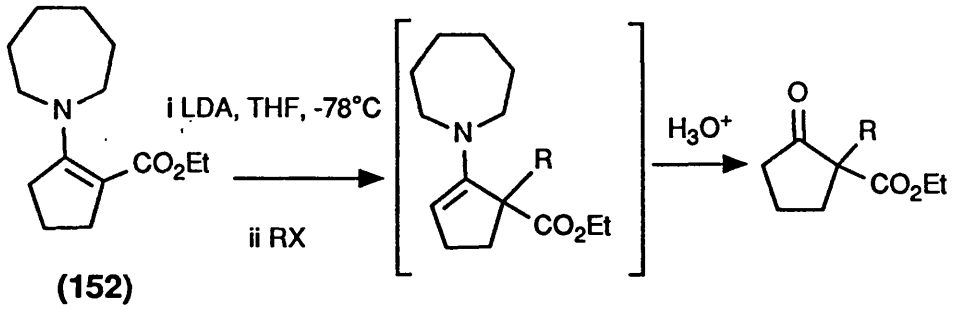
(150)

entry	RX		yield(nmr)
1	MeI	**(154)**	0
2	MeI / DMPU	**(154)**	0
3	 / DMPU	**(155)**	100%
4	 /DMPU	**(156)**	50% (16%isolated)



(151)

5	MeI	**(154)**	0
6	MeI / DMPU	**(154)**	90%
7		**(155)**	40%



(152)

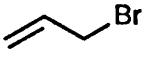
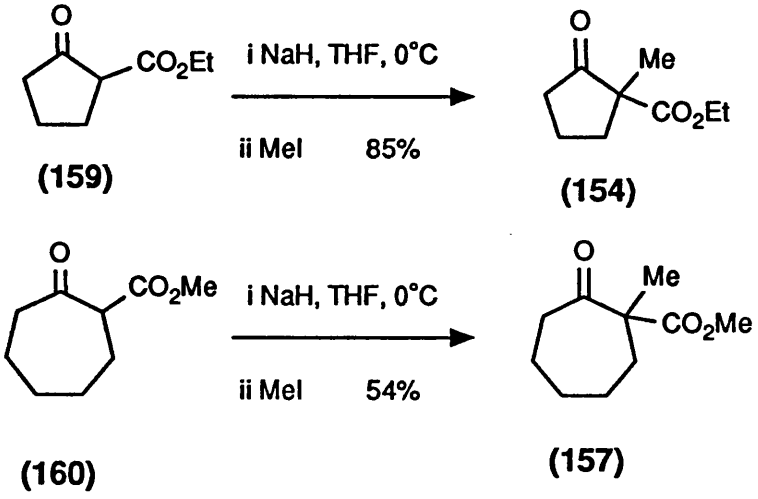
8	MeI / DMPU	**(154)**	43%
9	 / DMPU	**(155)**	100%

Table 10

To summarize, α-alkylation of cyclohexanonecarboxylate can be effected *via* the enamine anion, independent of the amine ring size and hence, the tendency to unconjugation. This provides a method for the regiospecific α-alkylation of the β-keto ester.

The effect of β-keto ester ring size was investigated by studying the reactions of the anions of the enamines of the cyclopentane and cycloheptanone derived β-keto esters **(150-152)** and **(153)**. The results are shown in Tables 10 and 11. In all the cases studied, the α-alkylated product was formed exclusively.

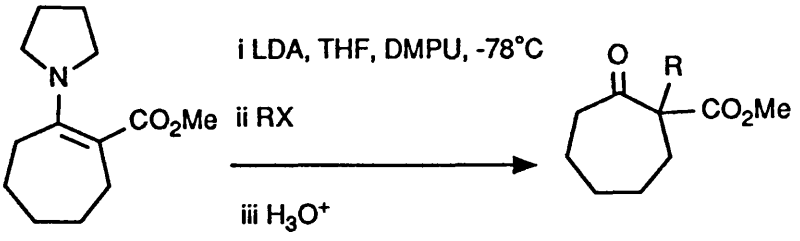
Authentic samples of α-methylated products **(154)** and **(157)** were prepared by alkylation of the parent β-keto esters, **(159)** and **(160)**. (Scheme 95).



Scheme 95

The authentic product **(154)** was shown to be identical to the product of the reaction of the enamine anion with iodomethane (entries 6 and 8, Table 10), by g.c. and ^1H nmr. Comparison of the nmr data with that reported in the literature for the γ-alkylated product ethyl 3-methylcyclopentanone carboxylate[106] confirmed that none was present.

The alkylated product **(155)** was assigned as the α-product by comparison of the



(153)

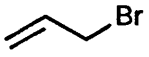
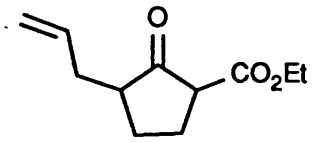
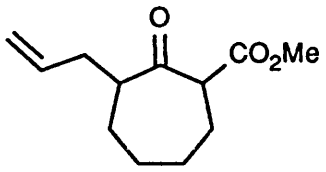
RX		
MeI	**(157)**	70% (nmr)
	**(158)**	67% (nmr), 30% (isolated)

Table 11

nmr data with the literature data for **(155)**[107] and the γ-alkylated product **(161)**.[80]



(161)



(162)

The results in Table 10 demonstrate that the size of the amine ring influences the reactivity of the enamine anion. The anion of pyrrolidine enamine **(150)** will not react with iodomethane under any conditions (entries 1 and 2), whilst the anion of piperidine enamine **(151)** reacts with iodomethane in the presence of DMPU (entry 6) and with allyl bromide in the absence of DMPU (entry 7). The anion of the cycloheptane derived enamine **(153)** will only react with alkyl halides with DMPU present as a cosolvent; and again reaction occurs exclusively at the γ-position. (Table 11) The role of DMPU in increasing the reactivity of the anions of the enamines in the alkylation reaction is not understood.

The regioselectivity of alkylation of the enamine **(153)** was again proven by comparison of the reaction product with the authentic sample of α-methyl ester **(157)** by g.c. and nmr. The structure of the α-alkylated product **(158)** was confirmed by comparison of the nmr data with the literature data for the γ-alkylated product **(162)**[80].

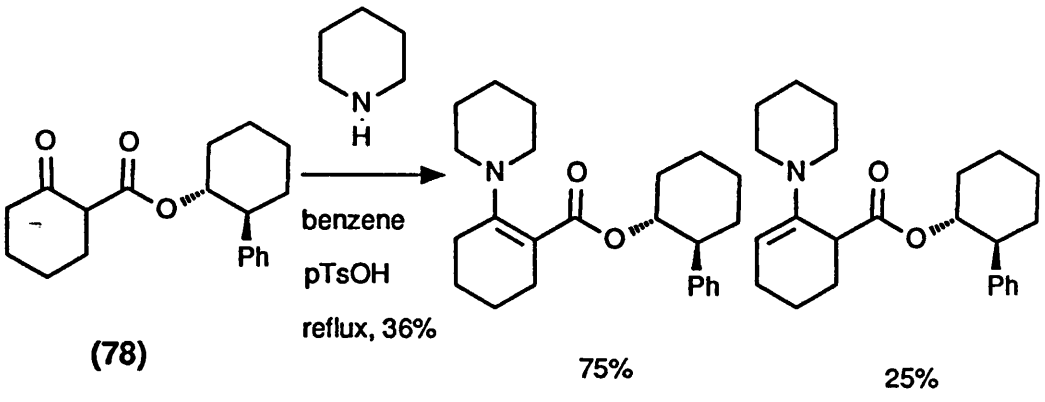
The alkylation reaction of the allylic anion derived from enamines of cyclic β-keto esters appears to be general for a range of β-keto ester ring sizes. This represents a method for the regiospecific alkylation of β-keto esters at the α-position avoiding the problems associated with alkylation of metal enolates.

It is complementary to the direct enamine alkylation developed by Gravel and Labelle[80] which gave γ-alkylated products.

The reactivity of these enamine anions can be contrasted with other heteroatoms substituted allylic anions.[90-95, 99-103]

3.4 ASYMMETRIC ALKYLATION VIA ENAMINES OF CHIRAL β-KETO ESTERS?

The asymmetric alkylation of β-keto esters was the ultimate aim of this project. Therefore, we prepared the enamine of the chiral β-keto ester **(78)** using the standard method. (Scheme 96).

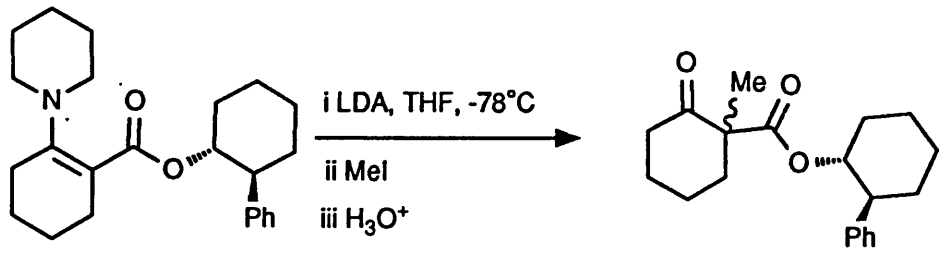


Scheme 96

The enamine **(163)** was prepared in 36% yield (after distillation) and the amount of unconjugated enamine was determined by nmr to be 25% (δ_H 4.75, 0.25H, t, *J* 4Hz, -CH=C-N-). Somewhat surprisingly, the enamine exists predominantly in its conjugated form and this is in marked contrast to the piperidine enamine of ethylcyclohexanone carboxylate **(139)** (75% unconjugated).

The enamine was deprotonated with LDA in THF at -78°C and the anion

reacted with iodomethane. Hydrolysis of the resulting enamine revealed the β-keto ester **(80)**, methylated at the α-position in 40% yield but as a 1:1 mixture of diastereomers. The product was shown to be identical to an authentic samples of **(80)** prepared previously (see Scheme 45) (Scheme 97).



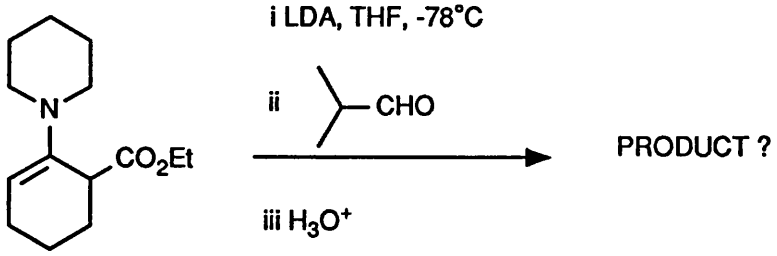
(163) **(80)** 1:1

Scheme 97

3.5 ATTEMPTED ALDOL REACTIONS OF ENAMINES OF CYCLIC β-KETO ESTERS

Schlessinger[99-102] investigated the reactivity of the anions of acyclic β-keto ester enamine **(128)** with isobutyraldehyde and observed exclusive reaction at the γ-position. Therefore, we looked at the aldol reaction of the anions of cyclic β-keto ester enamines.

Under the usual reaction conditions the enamine **(139)** did not react with either benzaldehyde or cyclohexanone. However, with isobutyraldehyde a product was formed. (Scheme 98).

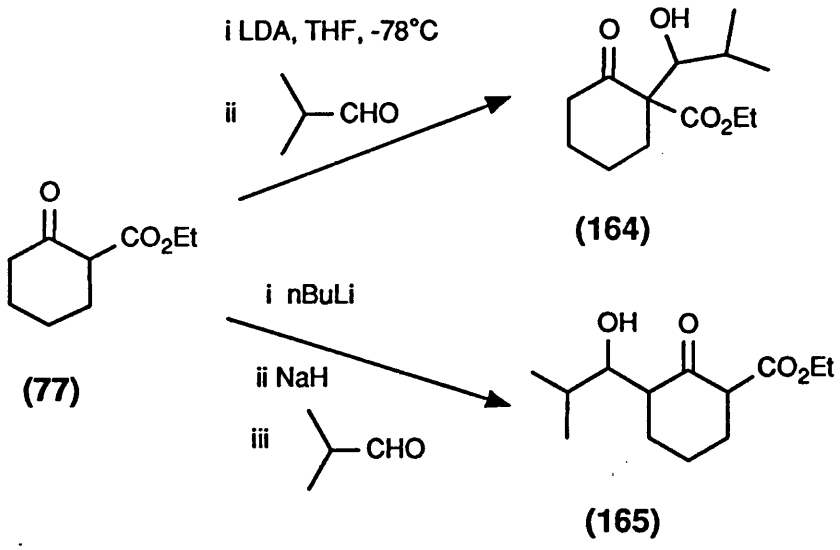


(139)

Scheme 98

This product has resisted identification to date. The ^1H nmr spectrum shows that the product does not contain an ethyl ester.

Attempts were made to prepare the expected α or γ products from the β-keto ester (**77**) by standard methods deprotonation with LDA and trapping with isobutyraldehyde to give the α-product (**164**) or formation of the dianion and reaction with isobutyraldehyde to give the γ-product (**165**).[83] (Scheme 99).



Scheme 99

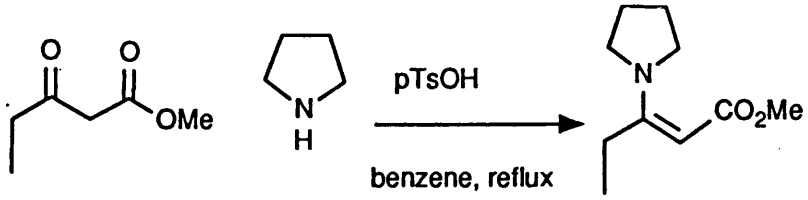
However, neither the ^1H nmr spectra from the reactions or from subsequent exposure of the products to the hydrolysis conditions yielded any useful information and this investigation was abandoned.

3.6 REGIOSELECTIVITY OF ALKYLATION OF THE ANIONS OF ACYCLIC ENAMINOESTERS

Schlessinger had investigated the regioselectivity of aldol reaction of the lithium enolate derived from the acyclic enaminoester (**128**),[99,100] however, he had not reported any alkylation reactions of this system. Therefore, we studied

the regioselectivity of alkylation.

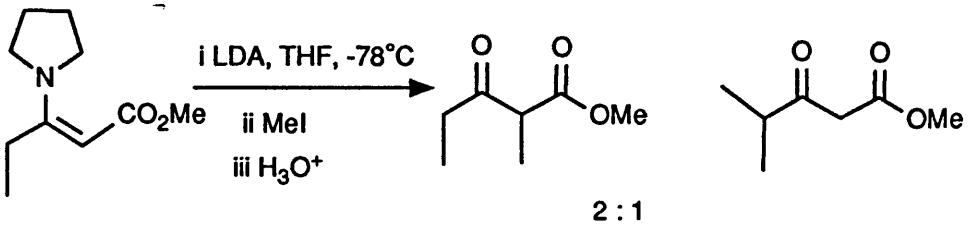
The pyrrolidine enamine **(128)** was readily prepared from methyl propionylacetate in good yield (Scheme 100).



(128)

Scheme 100

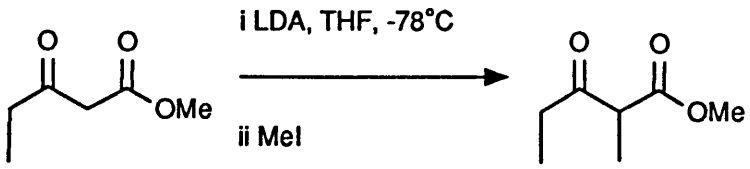
The enamine **(128)** was deprotonated with LDA in THF at -78°C and trapped with iodomethane and hydrolysed with dil. hydrochloric acid. The crude reaction mixture was analysed by ^1H nmr and found to be a 2:1 mixture of α-alkylated product **(166)** and γ-alkylated product **(167)** (Scheme 101).



(128) **(166)** **(167)**

Scheme 101

This was confirmed by comparison with an authentic sample of **(166)** prepared from methyl propionyl acetate (Scheme 102) and the ^1H nmr data reported in the literature for γ-product **(167)**.[108]



(166)

Scheme 102

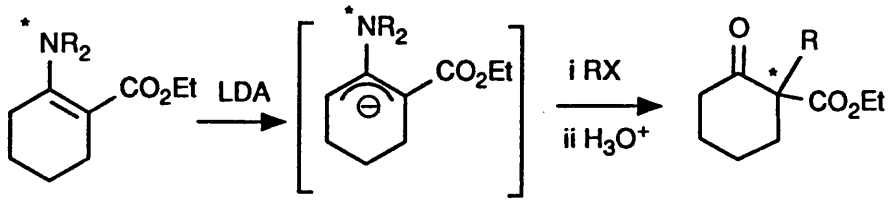
There was little regioselectivity observed in the reaction of the enolate of enamine **(128)** with iodomethane in contrast to the regioselectivity shown in the reaction with isobutyraldehyde. Similar results have been observed with other heteroatom substituted allylic anions where the regioselectivity depends on the nature of the electrophile.[109]

Further investigations with a wider range of electrophiles are needed to define the reactivity of the allylic anion of the enamine **(128)**.

ASYMMETRIC ALKYLATION VIA β-KETO ESTER ENAMINES

4.1 C_2-SYMMETRIC AMINES AS CHIRAL AUXILIARIES

In Chapter 3, we demonstrated that cyclic β-keto esters undergo selective α-alkylation in good yield *via* the allylic anion **(169)** of β-keto ester enamines **(168)**. Having established the regioselectivity of this reaction, we wished to investigate the potential for asymmetric alkylation by incorporation of a chiral amine into the enamine component. (Scheme 103).

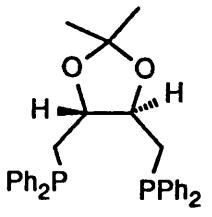


(168) **(169)**

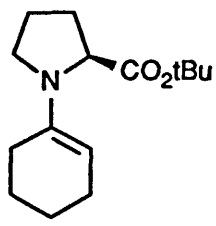
Scheme 103

Many amines have been employed as chiral auxiliaries in asymmetric synthesis. However, recently, the use of compounds containing a C_2 axis of symmetry as chiral auxiliaries has attracted much interest.[110] In general, higher levels of stereodifferentiation have been observed with auxiliaries containing a C_2 symmetry element as compared to those with no symmetry.

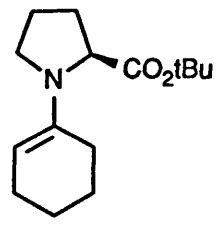
Historically, the first C_2-symmetric chiral auxiliary, DIOP **(170)** was reported by Kagan[111] in 1972.



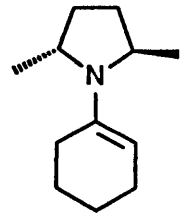
(170)



(171a)



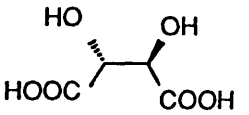
(171b)



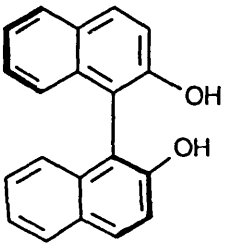
(172)

73.

This report led to the development of a range of 'bidentate' C_2 symmetric chiral auxiliaries based on the tartaric acid and binaphthol skeletons. However, the development of 'monodentate' C_2 symmetric auxiliaries has been slower.

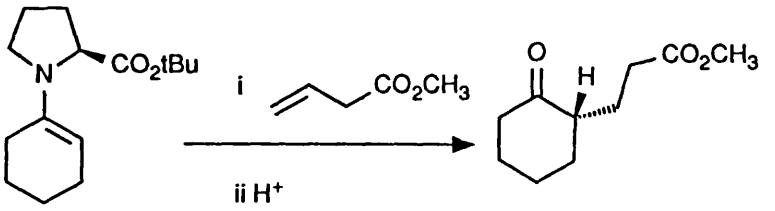


tartaric acid



binaphthol

In 1969, Yamada[112] reported the asymmetric alkylation of a chiral enamine **(171)** incorporating a proline derived chiral auxiliary; diastereoselectivities of up to 59% were observed but more typical values were in the 10-30% range (Scheme 104).



(171)

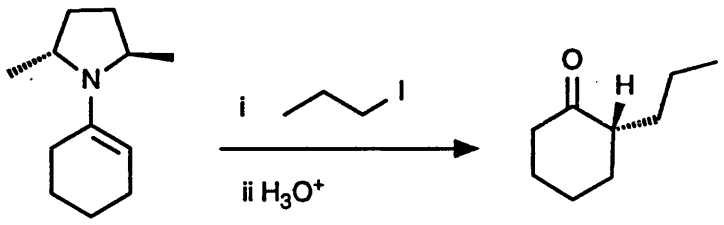
17%, 59% ee

Scheme 104

These results are consistent with the participation of two sets of transition states based on the two conformers of the enamine **(171a)** and **(171b)**. The ester group would be expected to exert a significant steric interaction in only one conformer **(171a)**; an enamine incorporating a C_2 symmetric chiral auxiliary **(172)** can exist as only one conformer.

This point was recognised by Whitesell[113] who observed: "Clearly, what is needed is an amine with a C_2 axis of symmetry". Indeed, the enamine **(172)**

derived from (+)-trans-2,5-dimethylpyrrolidine underwent alkylation with iodopropane with an enantiomeric excess of 93%. (Scheme 105).This represents the first example of a 'monodentate' C_2-symmetric chiral auxiliary in asymmetric synthesis.

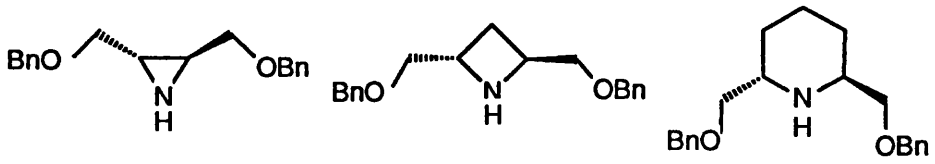


57%, 93% ee

(172)

Scheme 105

A range of C_2-symmetric amines both cyclic and acyclic, have now been prepared and their potential in asymmetric synthesis investigated. The cyclic amines based on the pyrrolidine ring have found the most widespread applicability but recently routes to aziridine **(173)** [114], azetidine **(174)**[114] and piperidine **(175)**[115] have been reported.

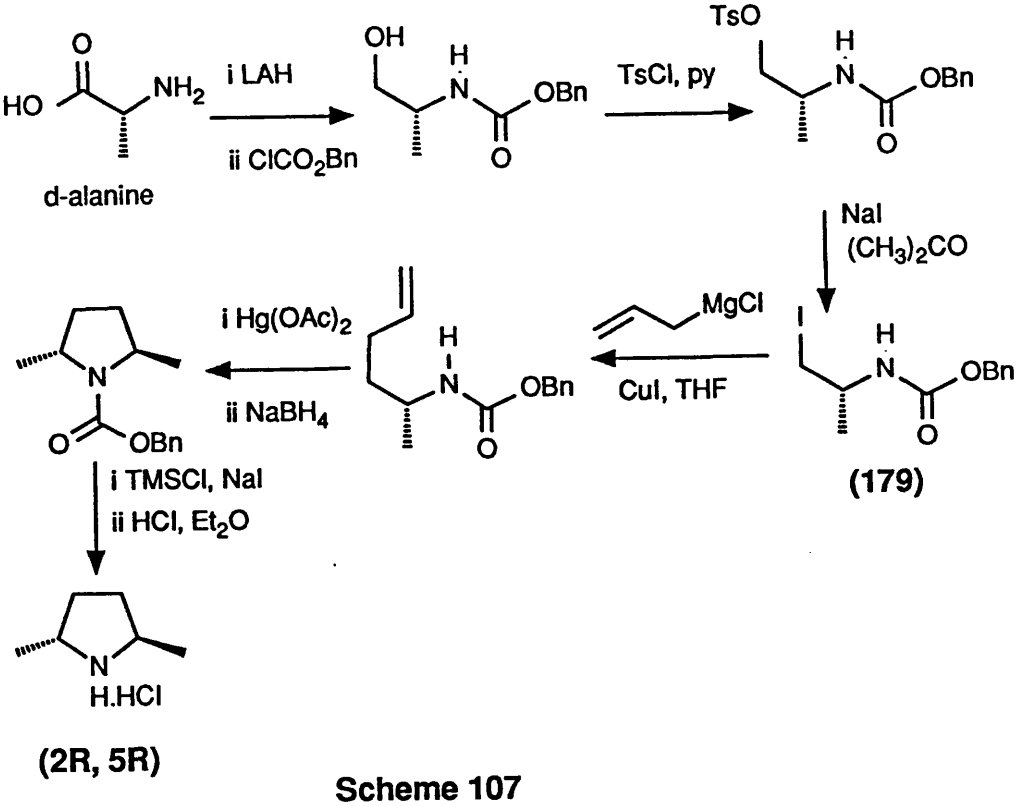


(173) **(174)** **(175)**

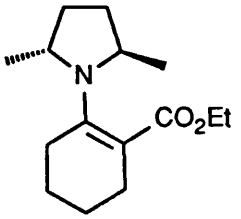
4.2 TRANS-2,5-DIMETHYLPYRROLIDINE

We focused on 2,5-dimethylpyrrolidine as a chiral auxiliary for asymmetric alkylation of β-keto esters and hence, we identified enamine **(176)** as our initial target for this aspect of the project.

There are, however, limitations to the use of 2,5-dimethylpyrrolidine as a chiral auxiliary, despite the impressive levels of asymmetric induction


HO
O
NH2
d-alanine
i LAH
ii ClCO2Bn
OH
H
N
OBn
O
TsCl, py
TsO
H
N
OBn
O
NaI
(CH3)2CO
I
H
N
OBn
O
(179)
MgCl
CuI, THF
i Hg(OAc)2
ii NaBH4
N
O
OBn
i TMSCl, NaI
ii HCl, Et2O
N
H.HCl
(2R, 5R)

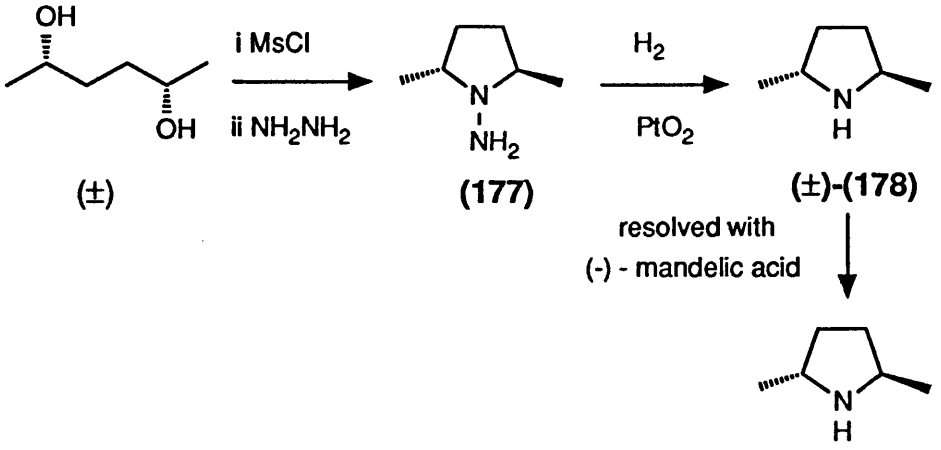
Scheme 107



(176)

observed by Whitesell[113] and Schlessinger[101] (see, Scheme 86, Chapter 3). The amine is not commercially available and the number of reports of the use of this amine remains low, which is probably associated with the relative difficulty of preparing 2,5-dimethylpyrrolidine.

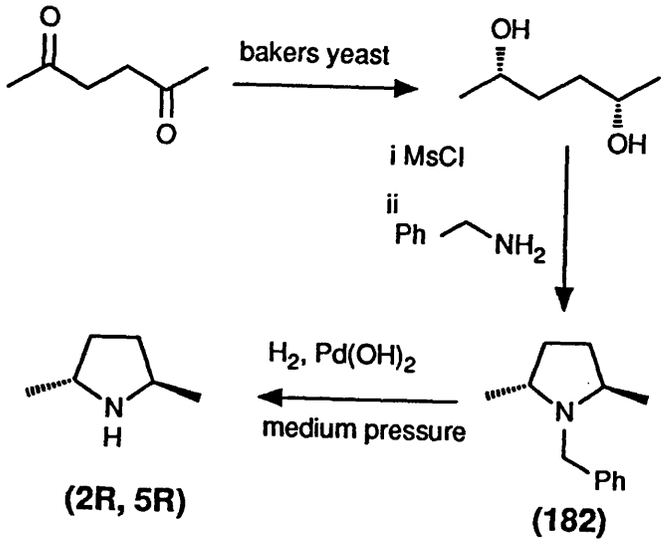
A number of approaches to 2,5-dimethylpyrrolidine have been described. Whitesell[113] prepared (+)-**(178)** *via* catalytic reduction of N-aminodimethylpyrrolidine **(177)**[116] and resolution with mandelic acid. (Scheme 106).



Scheme 106 **(+)-(178)**

Schlessinger developed an asymmetric synthesis of 2,5-dimethylpyrrolidine starting from the appropriate enantiomer of alanine.[117] (Scheme 107).

The overall yield for the reaction sequence is an impressive 44%. However, Schlessinger comments that the coupling of allyl magnesium chloride with iodide **(179)** can be a capricious step. The trans stereochemistry is established using the intramolecular amidomercuration procedure of Harding.[118]

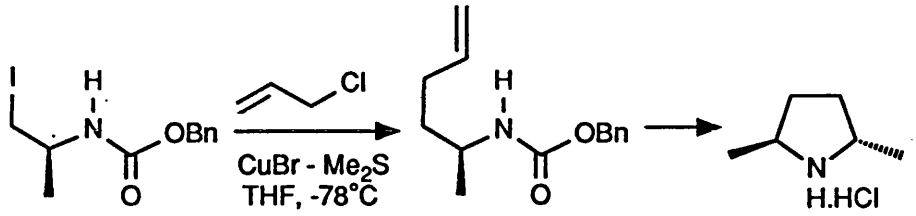


(2R, 5R)

(182)

Scheme 109

Very recently, an optimized synthesis of (2S, 5S)-2,5-dimethylpyrrolidine based on the route of Schlessinger has been reported,[119] which focused on the difficult cuprate reaction. (Scheme 108).

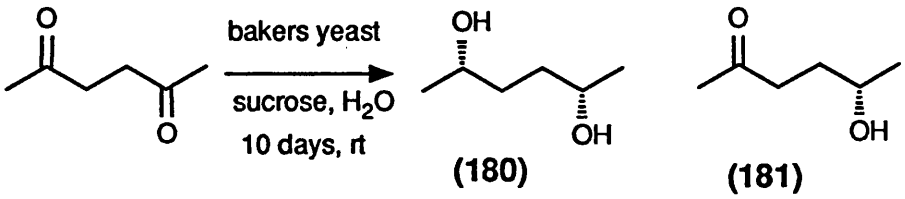


(2S, 5S)

Scheme 108

The synthesis of (2R, 5R)-2,5-dimethylpyrrolidine has been elegantly achieved by Masamune.[120] The synthesis utilizes (+)-(2S,5S)-2,5-hexanediol as the starting material obtained by asymmetric reduction of 2,5-hexanedione with bakers yeast.[121] (Scheme 109).

We decided to pursue the Masamune route to prepare 2,5-dimethylpyrrolidine. Bakers yeast reduction of 2,5-hexanedione following the procedure of Lieser[121] gave a 1:1 mixture of diol **(180)** and hydroxyketone **(181)** after 10 days. (Scheme 110).



(180) **(181)**

Scheme 110

After 72h, all the starting hexanedione had been consumed as judged by TLC and the hydroxyketone **(181)** was observed as the sole product. As time progressed, the formation of the diol **(180)** can be observed by TLC but the reaction never proceeded beyond a 1:1 mixture of **(180)** and **(181)**. After work

up, diol **(180)** was crystallized from the crude product and then purified by recrystallisation to give the (+)-diol **(180)** in 15% yield; m.p. 52-53°C $[\alpha]^{20}_D$ + 34.7° (*c*, 9.5, $CHCl_3$) [Lit[122]; mp 53-53.5°C $[\alpha]^{25}_D$ + 35.1° (*c*, 9.49, $CHCl_3$)]. The low recovery of the diol reflects the difficulty of extracting this material from the aqueous medium - a one mole scale reduction requires 20 litres of water.

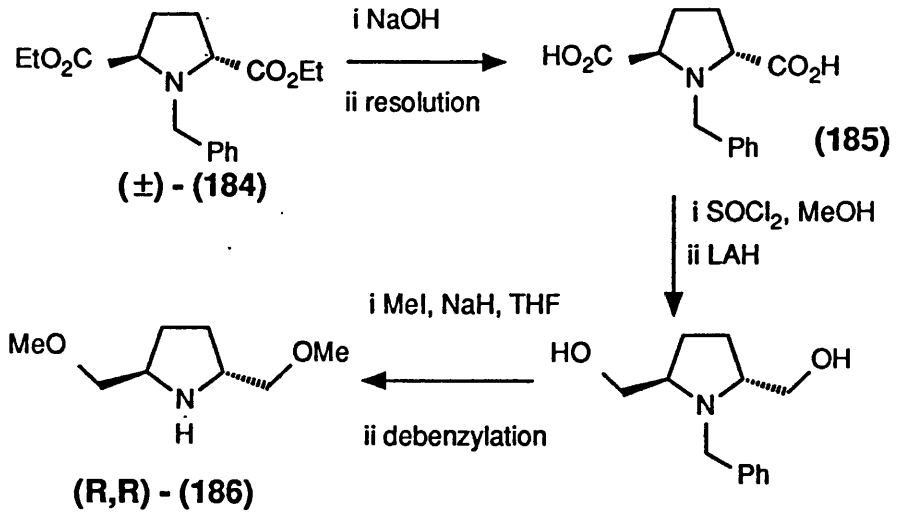
Mesylation and treatment with benzylamine following the procedure of Masamune resulted in formation of the pyrrolidine **(182)** in 52% yield after distillation.

Masamune removed the benzyl group of **(182)** by medium - pressure hydrogenolysis over Pearlman's catalyst ($Pd(OH)_2$-C); on a large scale (0.2 mol) (-)-dimethylpyrrolidine **(178)** was isolated in 94% yield after a careful distillation.

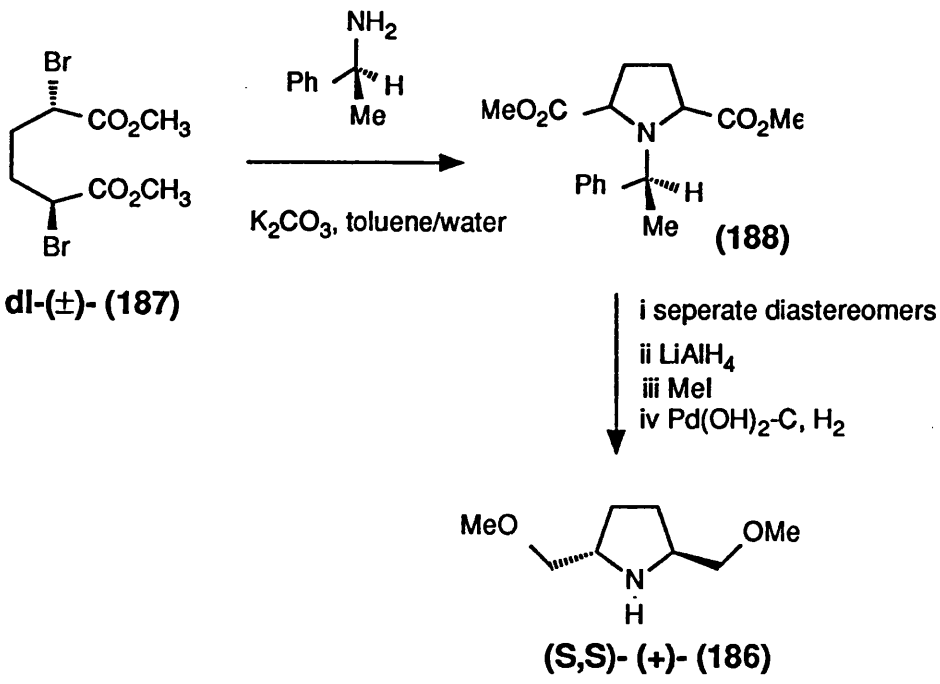
However, when we attempted this on a small scale (0.02 mol), it was impossible to isolate any product using the procedure probably due to the volatility of the amine **(178)** (b.p. 102-103°C).

We found that the benzyl group could be removed by hydrogenolysis at atmospheric pressure over Pearlman's catalyst in methanol.[123] (Scheme 111). The pyrrolidine **(178)** was isolated as its hydrochloride salt **(183)** and purified by recrystallisation. (m.p. 196-198°C, $[\alpha]^{20}_D$ + 5.0° (*c*, 3.0, CH_2Cl_2)) [lit[117]; m.p. 197-200°C, $[\alpha]^{20}_D$ + 5.47° (*c*, 3.0, CH_2Cl_2)]).

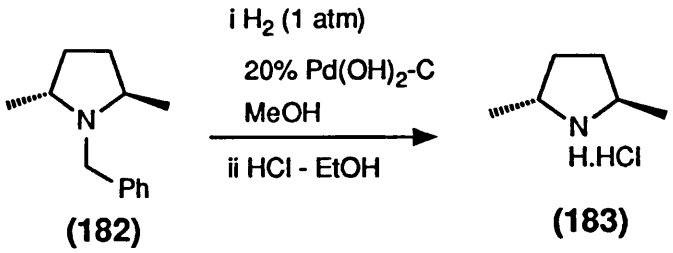
Hence, (-)-(2R, 5R)-2,5-dimethylpyrrolidine was prepared but in low yield. As only small quantities of dimethylpyrrolidine were available, it was necessary to use a more readily available C_2-symmetric amine as a model



Scheme 112



Scheme 113



(182) (183)

Scheme 111

compound to develop the asymmetric alkylation and minimise the waste of the precious (-)-(2R, 5R)-2,5-dimethylpyrrolidine.

4.3 TRANS -2,5-BIS(METHOXYMETHYL)PYRROLIDINE

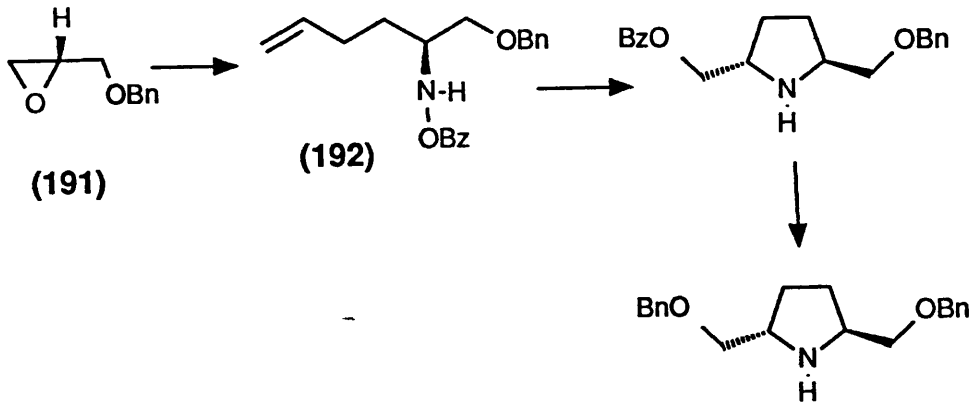
Trans 2,5-bis(methoxymethyl) pyrrolidine was introduced as a C_2-symmetric chiral auxiliary by Katsuki in 1984[124], and it has found a number of applications resulting in high levels of asymmetric induction.[110,125,126]

A number of groups have reported approaches to bis(methoxymethyl)pyrrolidine, although when we started this work, only the route of Katsuki had been published.

Katsuki outlined a preparation of bis(methoxymethyl)pyrrolidine from the racemic diester **(184)**.[124] (Scheme 112). The pyrrolidine **(186)** was available in enantiomerically pure form by resolution with D-(-)threo-(p-nitrophenyl)-2-amino-1,3-propanediol, of the diacid **(185)**.

Recently, Yamamoto[127] has reported a related method which avoids the resolution step. The racemic diester **(187)** was treated with (-)-phenylethylamine to form the pyrrolidine **(188)** as a mixture of diastereomers which were separable by chromatography. (Scheme 113).

Ghosez has also reported an 'improved' synthesis of



(191)

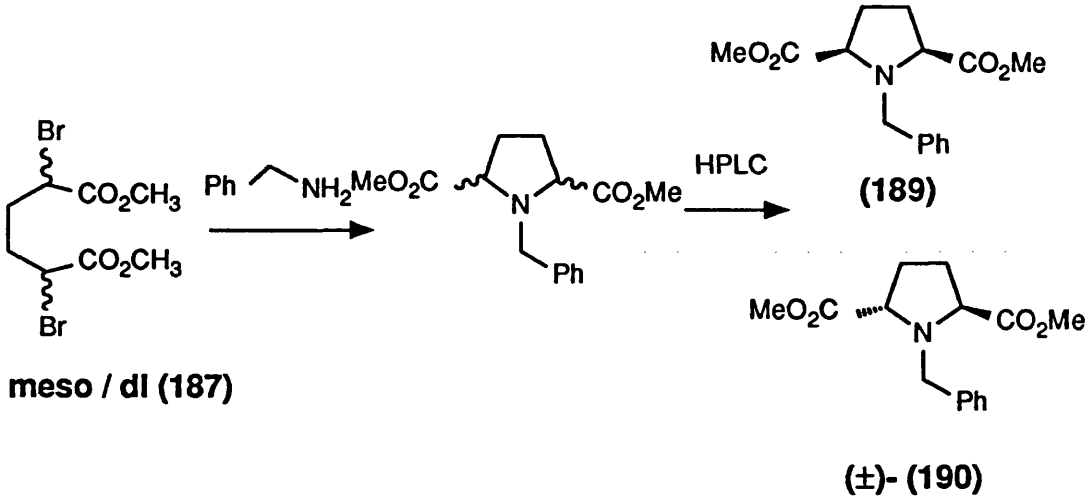
(192)

(-)- (193)

Scheme 115

bis(methoxymethyl)pyrrolidine[126] but the full experimental details have not yet been published but were obtained from the Louvain group.[128]

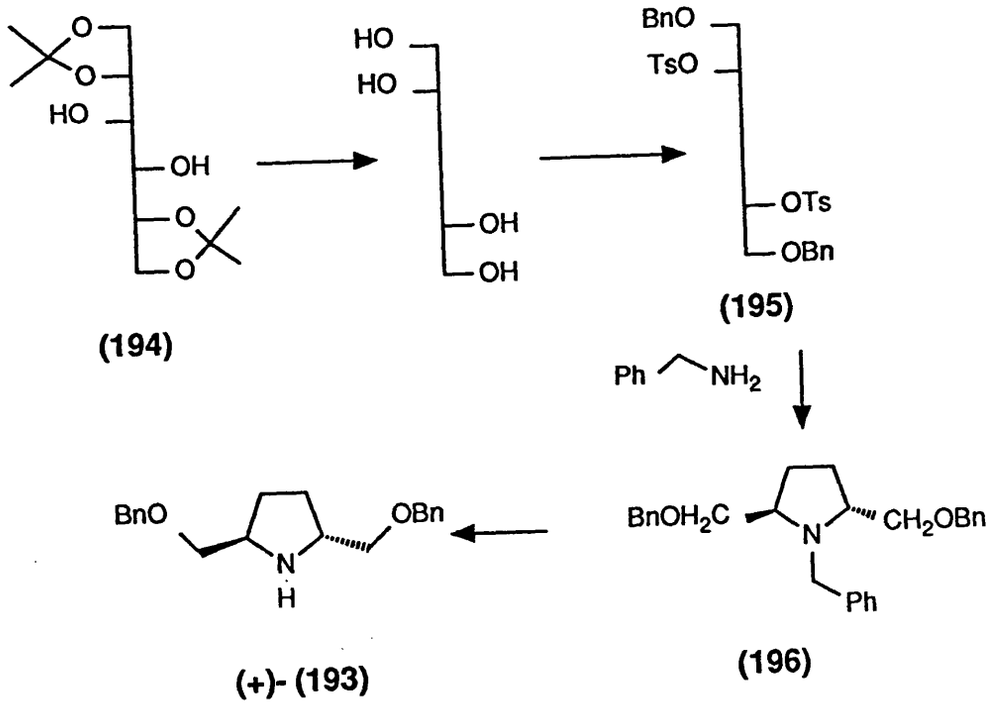
The basic strategy is the same as that of Katsuki. A mixture of the meso/dl-dibromodiester (**187**) was treated with benzylamine to give a mixture of the cis and trans pyrrolidines (**189**) and (**190**) which were then separated by preparative HPLC (Scheme 114).



Scheme 114

The trans isomer (±)-(**190**) was subsequently saponified to the diacid and resolved using ephedrine as the resolving agent to give the two enantiomers in >98% ee. Reesterification and reduction with lithium aluminium hydride yielded the diol. Methylation was effected in THF with iodomethane (3 equiv) and sodium hydride (12 equiv) as the base. Medium-pressure hydrogenolysis removed the benzyl group to yield the pyrrolidine (**186**) in optically pure form.

Two asymmetric syntheses of the related bis(benzyloxymethyl)pyrrolidine have been reported.Takano[129] utilised a stereoselective iodine-mediated cyclization of benzyloxyaminohexene (**192**) obtained from the enantiomerically pure glycidol (**191**) to prepare the trans 2,5-benzyloxymethyl pyrrolidine (-)-(**193**) (Scheme 115).



(194)

(195)

(196)

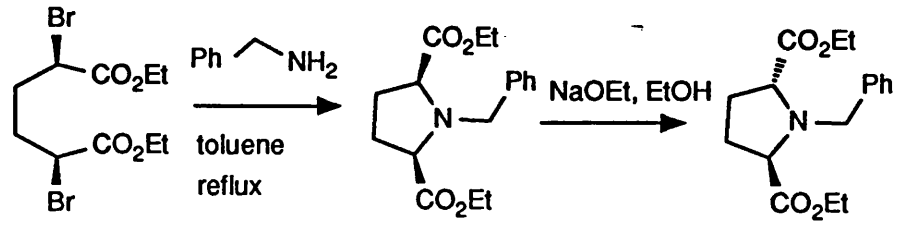
(+)- (193)

Scheme 116

Marzi and Misiti employed a carbohydrate precursor, 1,2:5,6 diisopropylidene mannitol **(194)** to prepare the key intermediate **(195)** which on treatment with benzylamine gave the N-benzylpyrrolidine **(196)** and debenzylation yielded the pyrrolidine (+)-**(193)**.[130] (Scheme 116).

When we started our investigations into the synthesis of bis(methoxymethyl)pyrrolidine, only the route of Katsuki had been reported although without full experimental details. We felt that we could adopt the same strategy to prepare large quantities of the racemic amine.

The starting material for Katsuki's route (Scheme 112) is the trans pyrrolidine diester **(184)**. This compound had been prepared by Lowe[131] by base catalysed epimerization of the cis-diester **(198)** prepared from meso-dibromoadipate[132] **(197)**. (Scheme 117).

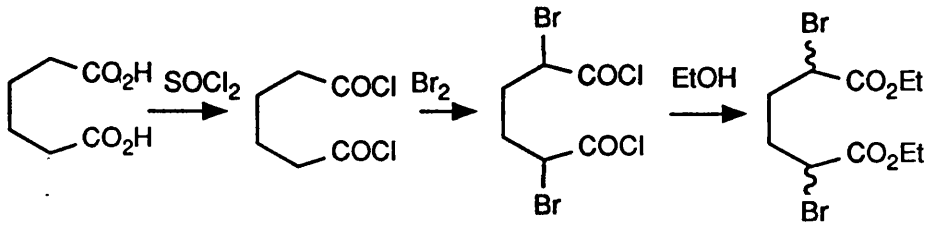


meso (197) **(198)** **(±)- (184)**

Scheme 117

We decided to pursue this route with some minor modifications. Diethyl dibromoadipate **(197)** is readily prepared from adipic acid as a mixture of meso and dl diastereomers.[133] (Scheme 118).

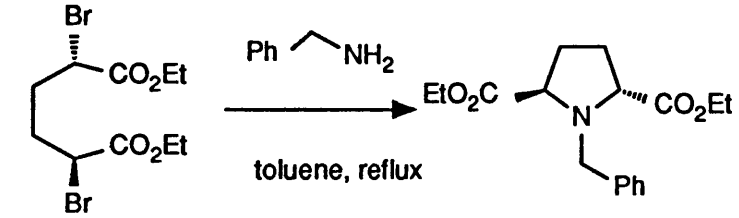
The meso diester crystallized from the crude product mixture, leaving the dl-diester as an oil. The dl-dibromoadipate was then treated with benzylamine under the conditions of Cignarella and Nathanson[132] to give the trans



(197)

Scheme 118

pyrrolidine diester **(184)** in 48% yield after purification by distillation. (Scheme 119).



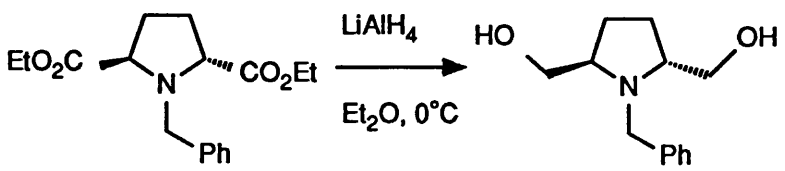
(±)- dl- (197) **(±)- (184)**

Scheme 119

The diester **(184)** was shown to be pure and not contaminated by the cis isomer **(198)** by conversion of the meso diester to **(198)** and comparison of the nmr spectra.[132]

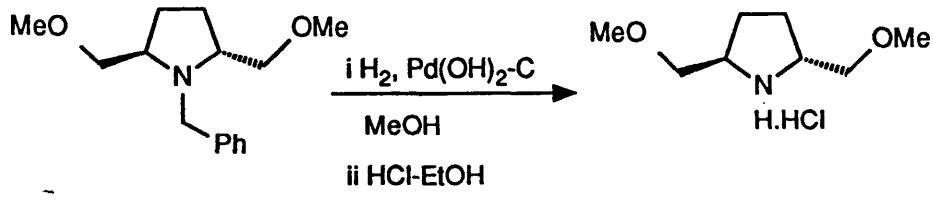
The epimerization of both the trans and cis pyrrolidines **(184)** and **(198)**[134] and meso and dl dibromoadipate **(197)**[135] has been studied and it is possible to interconvert the isomers by treatment with base.

The diester **(184)** was reduced with lithium aluminium hydride to give the diol **(199)** as an oil in 89% yield which was used without further purification. (Scheme 120).



(184) **(199)**

Scheme 120

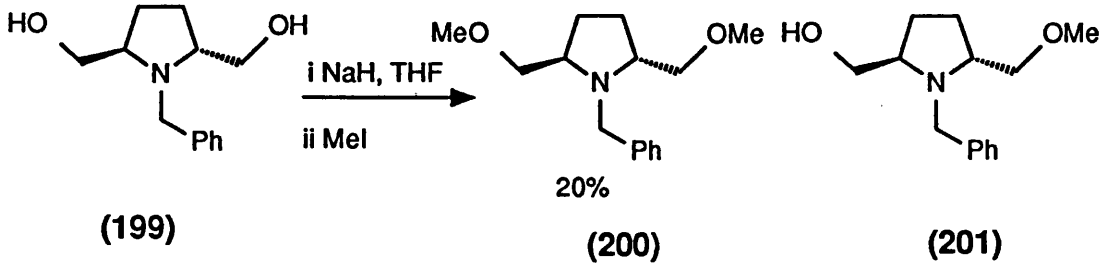


(200) **(±)- (202)**

Scheme 122

Methylation of this diol to give the bis(methoxymethyl)pyrrolidine (200) proved to be a rather troublesome step. Initial attempts to effect the etherification on a moderate scale (ca 20 mmol) using an excess of sodium hydride (3 equiv) and iodomethane (3 equiv) resulted in the formation of an insoluble colourless solid, which could not be identified but was assumed to be a quaternary amine salt, and an oil from which little useful product could be obtained.

Eventually, we found that the use of sodium hydride (1 equiv) and iodomethane (1 equiv) in THF at 0°C allowed preparation of bis(methoxymethyl)pyrrolidine (200) in low but reproducible yields on a small scale. The product was formed with monomethylated product (201) but could be purified by chromatography. (Scheme 121)



(199) (200) (201)

Scheme 121

Efforts to improve the yield of this transformation by use of other methylating agents (eg dimethyl sulphate) or bases (eg KF on alumina[136]) were not successful. Ghosez[128] has reported an 85% yield for the reaction using a large excess of sodium hydride (12 equiv) and iodomethane (3 equiv) on a large scale (0.28 mol). This was not tried but if reproducible would be the method of choice for this reaction.

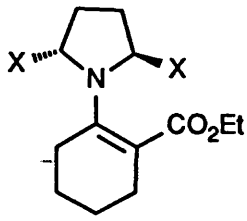
The benzyl group was removed by hydrogenolysis using the method of Yoshida,[123] and bis(methoxymethyl)pyrrolidine was isolated as the

corresponding hydrochloride salt (**202**). (Scheme 122).

A route to racemic bis(methoxymethyl)pyrrolidine has been established but the overall yield was low especially due to the problems of methylating the diol (**199**).

4.4 THE PREPARATION OF β-KETO ESTER ENAMINES

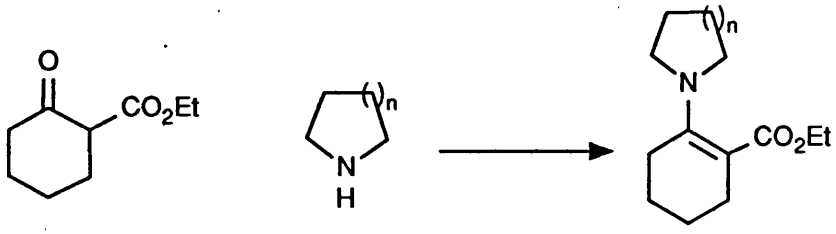
The availability of the C_2-symmetric amines, 2,5-dimethylpyrrolidine and 2,5-bis(methoxymethyl)pyrrolidine was hampered by the difficulties associated with the synthetic routes. Therefore, we needed a very efficient method for the preparation of enamines of type (**203**), which minimise the waste of the valuable pyrrolidines (**178**) and (**186**).



(**203**)

A number of considerations arose in the preparation of an enamine of this type. A practical problem was the relatively low boiling point of dimethylpyrrolidine (102-103°C); ideally, we needed a method for enamine preparation at an ambident temperature to reduce loss of the amine by evaporation. The rate of formation of the enamine would be slow due to steric hindrance from the bulky amine and the relatively unreactive carbonyl group of the β-keto ester.

The standard method for the preparation of an enamine, heating the β-keto ester, five equivalents of amine and catalytic p-toluenesulphonic acid to reflux as described in Chapter 3 is not an attractive route and the drawbacks are self



entry	amine	equiv	solvent	T / °C	dehydration method	t	yield
1	n=1	5	benzene	80	azeotrope	4.5h	70%
2	n=2	5	benzene	80	azeotrope	6 days	70%
3	n=1	1	ether	20	3Å ms	5 days	80%(gc)
4	n=2	1	ether	20	3Å ms	7 days	10%(gc)
5	n=1	6	hexane	50	$TiCl_4$	4h	95%(gc)
6	n=2	6	hexane	70	$TiCl_4$	4days	50%(gc)
7	n=1	2	hexane	70	$ClTi(O^iPr)_3$	4h	60%(gc)

Table 12

evident.

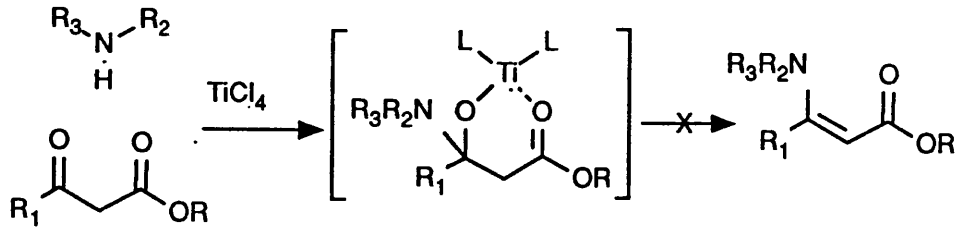
Therefore, we investigated other methods for the preparation of enamines; formation of both the piperidine and pyrrolidine enamines were investigated as models. We felt that piperidine represented a better steric model of the C_2-symmetric pyrrolidines than pyrrolidine itself. However, the rate of formation of the piperidine enamine was very slow, which is probably associated with its tendency to unconjugation.[85,86] We felt that the rate of formation of an enamine with a C_2 symmetric amine should, perhaps, be intermediate between pyrrolidine and piperidine.

The many available methods for the preparation of enamines have been reviewed.[137]

The most widely used method for the preparation of enamines involves condensation of an amine with a carbonyl compound. Azeotropic distillation has already been declared unsuitable, therefore, other dehydrating agents were considered and the results presented in Table 12.

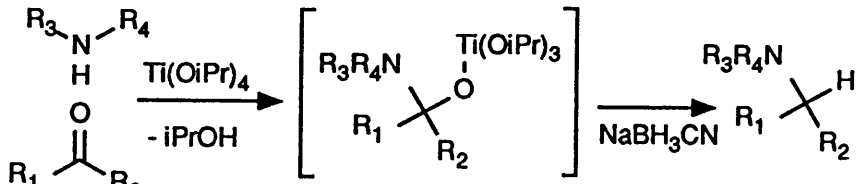
Molecular sieves have been used as a dehydrating agent in enamine synthesis.[133,138] This represents a very mild method for the preparation of enamines and can be effected at room temperature in a variety of solvents. This proved to be an efficient method for the preparation of the pyrrolidine enamine (entry 3, Table 12) but an impractically sluggish method for the preparation of piperidine enamine (entry 4). The yields were determined by g.c. and nmr analysis of the reaction mixture.

Another widely reported method for enamine formation involves the use of a titanium tetrachloride as a dehydrating agent and Lewis acid.[139] White has



(204)

Scheme 124



(205)

Scheme 125

suggested that the stoichiometry of the reaction is 3:1 amine to carbonyl. (Scheme 123).

$$2RCH_2COR^1 + 6HNR^2_2 + TiCl_4 \longrightarrow 2RCH{=}C(NR^2_2)R^1 + 4R^2_2NH.HCl + TiO_2$$

Scheme 123

Nilsson and Carlson reported an improvement of this procedure for the preparation of enamines of functionalized and sterically crowded carbonyl compounds.[140] An amine-titanium complex is formed by mixing titanium tetrachloride with the amine at 0°C in hexane, the carbonyl component is then added and the mixture heated. This method still requires a large excess (6 equiv) of amine with respect to the carbonyl component.

This method was applied (entries 5 and 6, Table 12) and appeared to proceed well by gc analysis of the crude reaction mixture for both pyrrolidine and piperidine cases. The work up procedure for this reaction essentially involves filtering the reaction mixture to remove titanium residues and removal of solvent under reduced pressure to give the crude enamine. However, this resulted in a very low recovery of material (<10%) which was shown by nmr to be the enamine.

The reaction proceeds via an intermediate complex **(204)** formed between the amine, carbonyl component and titanium. We suggest that when a β-keto ester is used as the carbonyl component, the additional carbonyl group can chelate to titanium which prevents breakdown of the complex to the enamine (Scheme 124).

A similar problem has been reported[141] in the reaction of a ketone with an amine using titanium IV isopropoxide as a Lewis acid, the enamine

functionality could not be observed by spectroscopic methods and an intermediate titanium species (**205**) was postulated which was reduced with sodium cyanoborohydride to give the amine. (Scheme 125)

The reaction using titanium tetrachloride as the dehydrating agent required a large excess of amine due to trapping of the reagent by HCl. (Scheme 123). Therefore, chlorotitanium triisopropoxide was investigated as a dehydrating agent. We presumed that the amine would displace chloride at titanium but not the isopropoxide ligands and, hence, only two equivalents of amine would be required.

Chlorotitanium triisopropoxide is readily prepared from titanium IV isopropoxide and titanium tetrachloride[142] (Scheme 126).

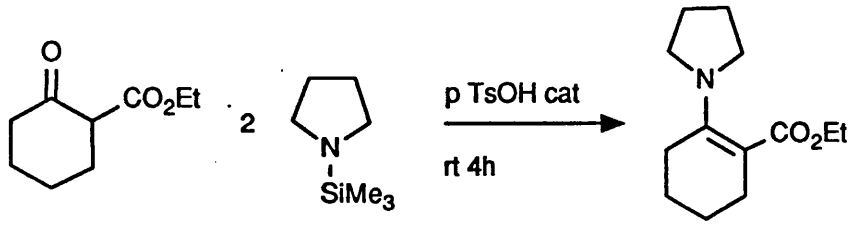
$$TiCl_4 + 3Ti(OiPr)_4 \longrightarrow 4ClTi(OiPr)_3$$

Scheme 126

Chlorotitanium triisopropoxide appeared to function as a dehydrating agent for the formation of the pyrrolidine enamine (entry 7, Table 12), however, the recovery of material after work up was again low.

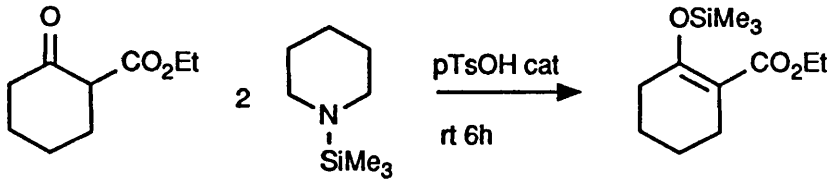
The formation of stable intermediate complexes appears to be a problem in the use of titanium reagents as dehydrating agents in enamine formation. The problem is perhaps exacerbated when using β-keto esters as the carbonyl component as the additional carbonyl group could provide extra coordination to titanium.

As the more familiar dehydration methods were not useful, we sought a more subtle approach to the problem of enamine preparation with β-keto esters.



(77) (148)

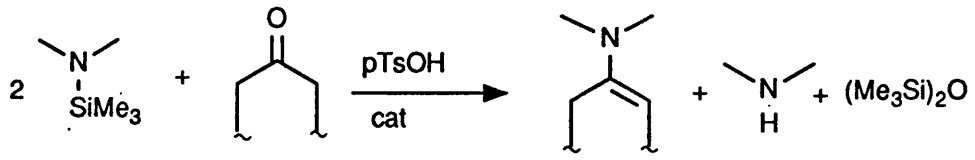
Scheme 129



(77) (89)

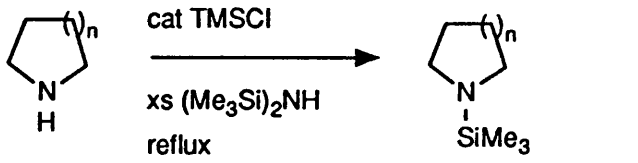
Scheme 130

Weinreb[143] reported a mild method for the formation of enamines especially with volatile amines. Treatment of a carbonyl compound with 2 equivalents of silylamine in the presence of a trace of p-toluenesulphonic acid but without added solvent provides the enamines in good yield (Scheme 127).



Scheme 127

Trimethylsilylpyrrolidine and piperidine were prepared using the method of Vorbruggen.[144] (Scheme 128).



n = 1, 48% n = 2, 61%

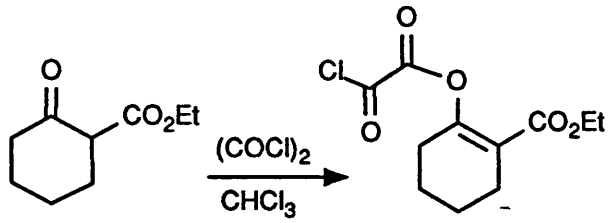
Scheme 128

This method of silylating amines would not be suitable for C_2-symmetric amines as the reaction is carried out in refluxing hexamethyldisilazane (155°C). However, a milder method for preparing silyl amines has been reported.[145]

The reaction between β-keto ester (**77**) and trimethylsilyl pyrrolidine yielded the enamine (**148**) in 75% yield (Scheme 129).

However, reaction of the ester (**77**) with trimethylsilylpiperidine gave the silyl enol ether (**89**) as the sole product (Scheme 130).

Hence, this method was discounted as a route for the preparation of C_2-symmetric enamines as it appeared that if formation of the enamine was



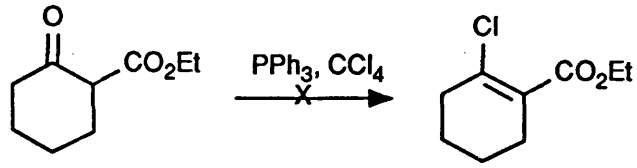
(207)

Scheme 132

slow, the silylated amine would react preferentially as a silyl transfer agent.

As an alternative to activating the amine, we investigated activating the carbonyl group by preparing the vinyl chloride (**206**). Enamine formation would occur via an addition-elimination mechanism.

A number of methods have been developed for converting carbonyl groups into vinyl halides. Triphenylphosphine/carbon tetrachloride[146] has been used to convert β-diketones to vinyl halides[147] but this reagent combination failed to react with β-keto ester (**77**). (Scheme 131)

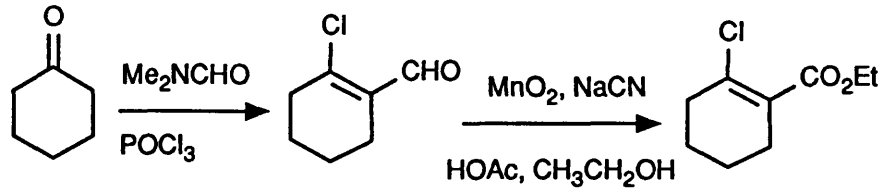


(**77**) (**206**)

Scheme 131

Heathcock has converted β-diketones to β-chloro vinyl ketones using oxalyl chloride in an inert solvent but reported that with β-keto ester (**77**) the product was the enolchlorooxalate (**207**).[148] (Scheme 132).

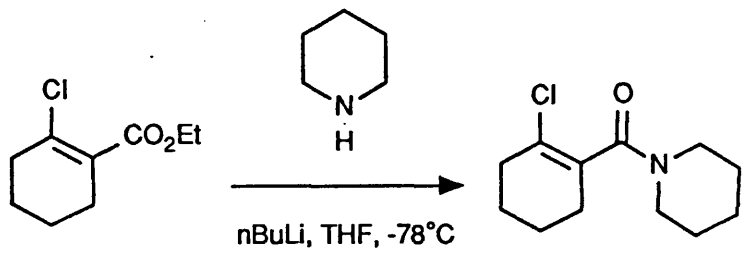
However, vinyl chloride (**206**) has been prepared[149] by oxidation[150] of the aldehyde (**208**) prepared from cyclohexanone in the Vilsmaier-Haack reaction.[151] (Scheme 133).



(**208**) (**206**)

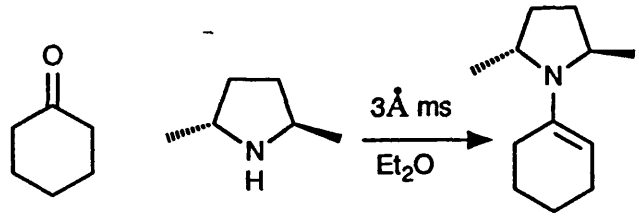
Scheme 133

de Ancos has reported the displacement of acyclic vinyl bromides with amines



(209)

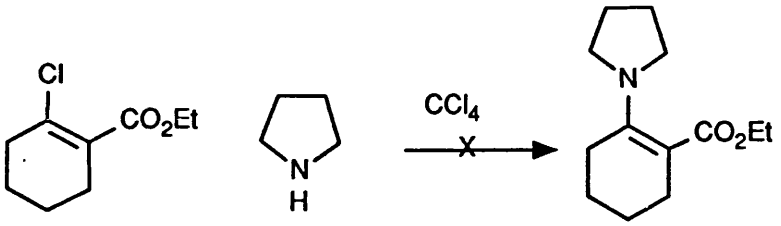
Scheme 135



(172)

Scheme 137

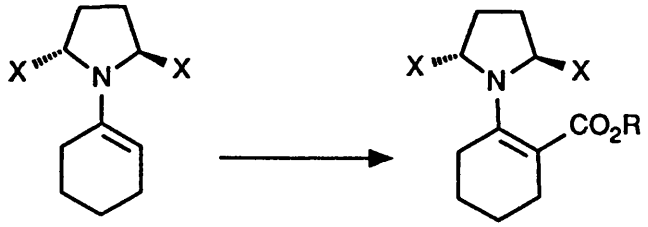
by simply stirring with the amine in carbon tetrachloride at room temperature.[152] However, attempts to displace the chloride of (**206**) under these conditions failed (Scheme 134).



Scheme 134

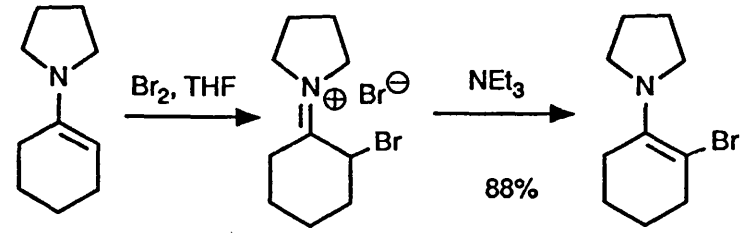
The displacement of a vinylic chloride has been effected using lithium piperidide.[153] The vinyl chloride (**206**) was added to a solution of lithium piperidide in THF at -78°C. A single product was obtained which was not the enamine but was tentatively assigned as the amide (**209**). (Scheme 135).The structure was assigned by the absence of the ethyl ester in the nmr spectrum and by mass spectral analysis [*m/z* 227 (45%), 229 15%) (M^+), 192 (100) (M^+-Cl)].As a result of our failure to prepare the required enamines, we abandoned this approach.

An alternative strategy based on the functionalization of an enamine derived from cyclohexanone was explored (Scheme 136).



Scheme 136

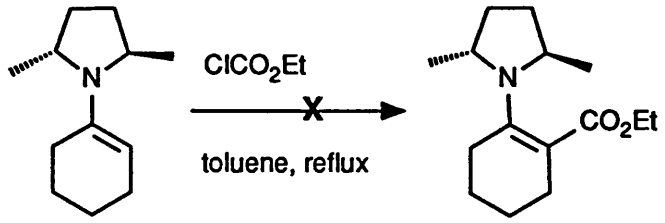
The enamine (**172**) derived from cyclohexanone and (-)-2,5-dimethylpyrrolidine was prepared following Whitesell's method,[113] using 3Å molecular sieves as the dehydrating agent (Scheme 137).



(210) (211)

Scheme 140

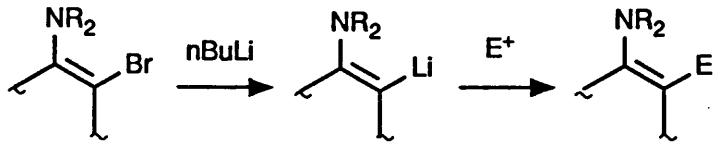
The acylation of enamine (**172**) with ethyl chloroformate was attempted.[154] Although this process is not regarded as an efficient method for acylation, we hoped that some of the desired enamine (**176**) might be formed (Scheme 138). However, no product was observed either by g.c. or nmr although we hope that further investigation of this reaction might be profitable.



(**172**) (**176**)

Scheme 138

An alternative method for the β-functionalization of enamines is *via* β-lithio enamines.[155] Duhamel has prepared β-lithio enamines *via* halogen-metal exchange.[156] (Scheme 139).

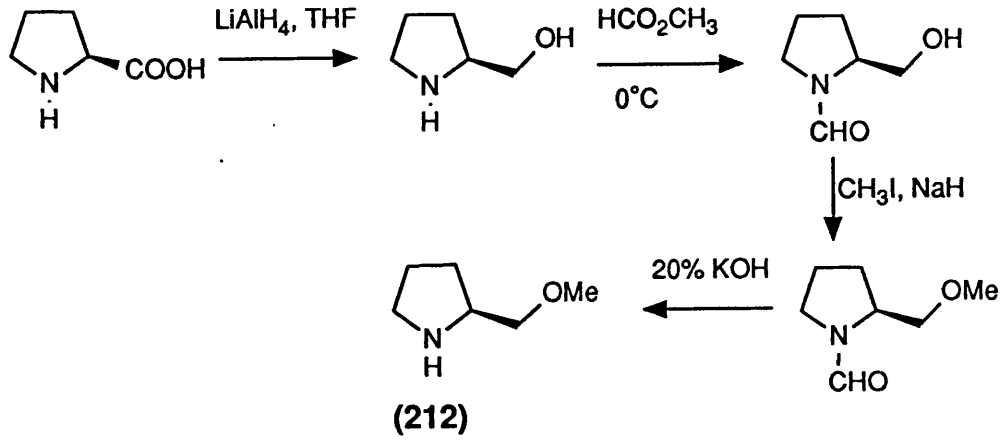


Scheme 139

The pyrrolidine enamine (**210**) was prepared and converted to the bromoenamine (**211**) in 88% yield by treatment with bromine and then triethylamine.[157] (Scheme 140).

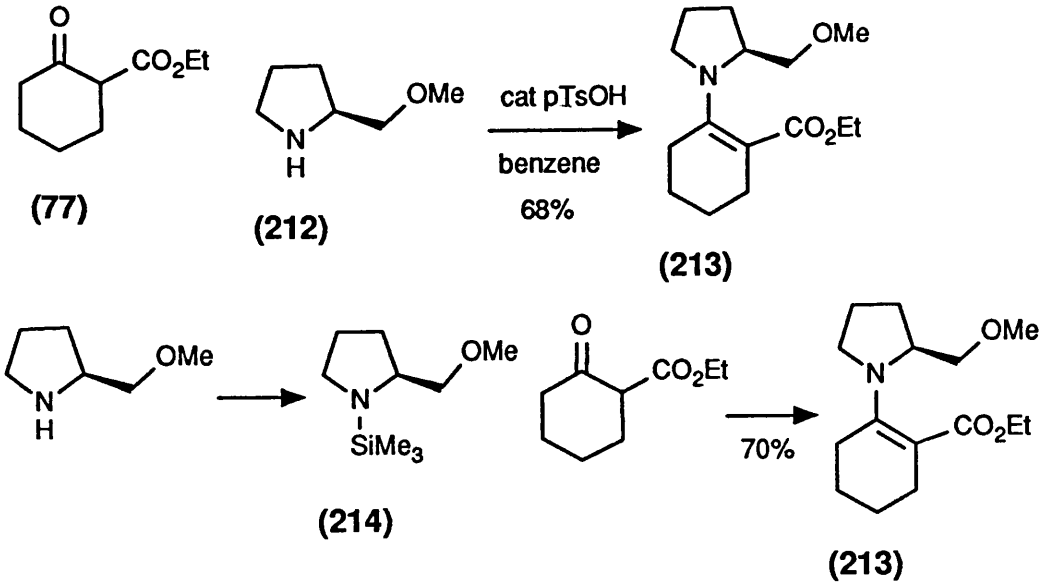
However, attempted halogen- metal exchange and trapping of the anion with iodomethane did not yield any identifiable products. Stork[158] has suggested that β-lithioenamines can be acylated so further investigation of this strategy may provide a route to the enamines of β-keto esters.

No satisfactory method for the preparation of enamines with C_2-symmetric amines was found and hence, this aspect of the project was abandoned until an



(212)

Scheme 141



(77) (212) (213)

(214) (213)

Scheme 142

efficient solution of this problem can be discovered.

4.5 (S)-METHOXYMETHYL PYRROLIDINE AS A CHIRAL AUXILIARY

(S)-Methoxymethylpyrrolidine is readily available from L-proline and has found wide use as a chiral auxiliary.

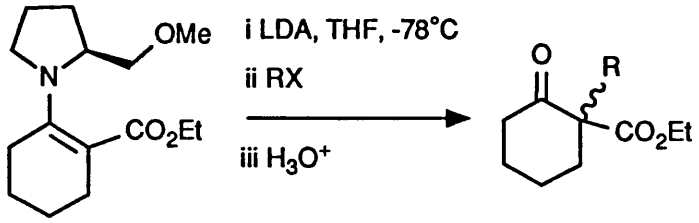
We decided to prepare the β-keto ester enamine with (S)-methoxymethylpyrrolidine to see if asymmetric alkylation could be effected.

(S)-Methoxymethypyrrolidine **(212)** was prepared following the procedure of Enders.[159] (Scheme 141).

Reduction of l-proline with lithium aluminium hydride gives prolinol which is formylated on nitrogen and methylated. Removal of the formyl group yields the pyrrolidine **(212)** which was purified according to the procedure of Seebach.[160] Vacuum distillation yielded an oil (61% from prolinol) [$[\alpha]^{20}_D$ + 8.22° (*c*, 1, $CHCl_3$); lit[160] : $[\alpha]_D$ + 3° (*c*, 2, benzene)].

The enamine **(213)** derived from pyrrolidine **(212)** and β-keto ester **(77)** was prepared either by heating the amine and carbonyl component in refluxing benzene with water separation or *via* the silylated amine[143] **(214)** prepared using the method of Vorbruggen.[144] (Scheme 142).

The enamine was shown to exist predominantly in the conjugated form (90%) (10% unconjugated) by integration of the enamine vinyl proton in the ^1H nmr spectrum (δ_H 4.5, 0.1H, t, *J* 4 Hz).



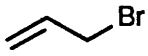
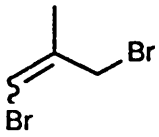
entry	RX		yield nmr	yield isolated	%ee	$[\alpha]_D$
1	MeI	**(142)**	40%	32%	33%	-7.8 °(c, 1.3, EtOH) R
2		/DMPU **(4)**	100%	40%	15%	+12 °(c, 2, $CHCl_3$) R
3		/DMPU **(143)**	67%	27%	15%	+2.5° (c, 9, $CHCl_3$)

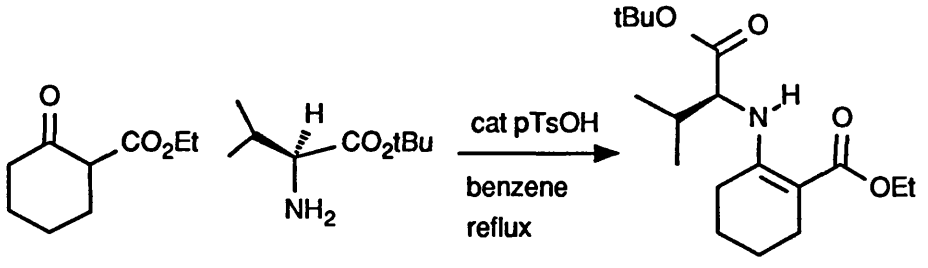
Table 13

Alkylation of enamine (**213**) was carried out under the standard conditions, deprotonation at -78°C with LDA and trapping with an alkyl halide, and the results are shown in Table 13.

The enantiomeric excess of the alkylation reaction with estimated by lanthanide induced chiral shift nmr using $Eu(hfc)_3$ as the resolving agent. For the α-methylated product (**142**), the methyl singlet (δ_H 1.26) was resolved into two signals (δ_H 1.82 and 1.78). With the allylated products (**4**) and (**143**), the determination of enantiomeric excess was more difficult as the resolved signals were multiplets ((**4**) - multiplet δ_H 5.08, 5.00 resolved δ 5.18 (0.6H, m), 5.10 (0.9H, m), 5.08 (0.6H, m) and (Z)-(143) methyl doublet δ 1.78 resolved to δ_H 1.84 (1.7H, d) and 1.78 (1.3H, d)). The absolute configurations of the products were deduced from the sign of the optical rotation by comparison with known compounds.

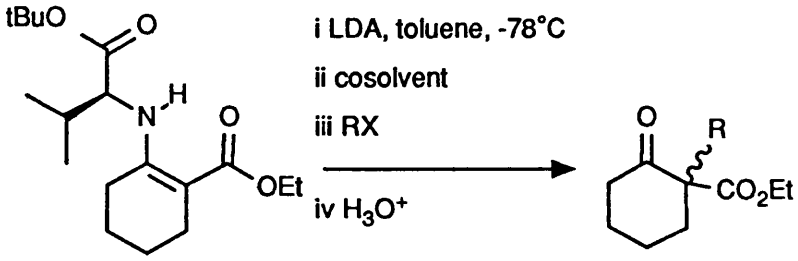
Authentic samples of enantiomerically enriched β-keto esters (**4**), (**142**) and (**143**) were prepared using the method of Koga.[5]

S-valine tert-butyl ester[162] was prepared from S-valine and isobutylene in the presence of conc sulphuric acid.[163] The enamine (**215**) was prepared using the standard method[6] in 92% yield [$[\alpha]^{22}_D$ +5.38°, (*c*, 2, $CHCl_3$)]. (Scheme 143).



(**215**)

Scheme 143



(215)

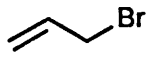
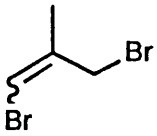
RX	cosolvent		yield	ee	$[\alpha]_D$
MeI	THF	**(142)**	50%	55%	+70 °(c 6 EtOH) S
	dioxolane	**(4)**	32%	-	+4.15° (c 2 $CHCl_3$) R
	dioxolane	**(143)**	54%	-	-2.1° (c 5 $CHCl_3$)

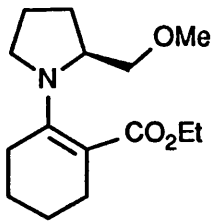
Table14

Deprotonation of the enamine (**215**) in toluene at -78°C and addition of a cosolvent and alkyl halide gave the alkylated β-keto esters. (Table 14).

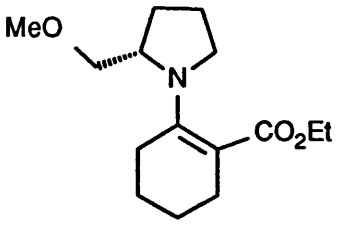
The enantiomeric excess was only measured in the case of ester (**142**). While the levels of asymmetric induction are much below those reported by Koga for the methyl ester, the sense of asymmetric induction as determined by the sign of the optical rotation is the same.

The use of (S)-methoxymethylpyrrolidine as a chiral auxiliary allowed asymmetric induction with a low level of enantioselectivity. It appears that the use of DMPU as cosolvent in the reaction resulted in a change in the stereochemical course of the reaction (entries 1 and 2, Table 13). However, the nature of the reactive species in the reaction is not known and must await further investigations in the reaction.

(S)-Methoxymethylpyrrolidine was investigated as a chiral auxiliary in order to ascertain the viability of our strategy for asymmetric alkylation using C_2 symmetric amines as chiral auxiliaries (Scheme 103). Although the levels of enantioselectivity in the reaction are low, they must be regarded as promising, for the reasons already outlined. The enamine (**213**) is predominantly conjugated (90%) and considering the two conformers (**213a**) and (**213b**) steric factors would suggest that conformer (**213b**) would be the major component.



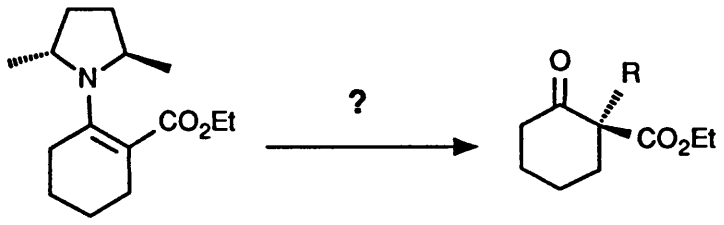
(213a)



(213b)

The chiral centre of the auxiliary is remote from the reacting centre, therefore, low levels of asymmetric induction must be expected. With a C_2-symmetric amine incorporated into the enamine (eg **(176)**) only one conformer is possible and a much higher level of asymmetric induction is expected.

Therefore, the problem has been redefined. We are confident that alkylation of the allylic anion of enamine **(176)** would lead to substituted β-keto esters with high enantiomeric excess (Scheme 144).



(176)

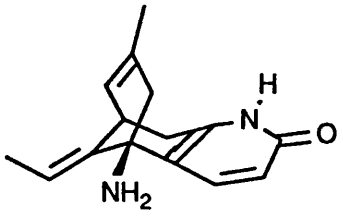
Scheme 144

However, the problem is now the efficient preparation of enamines derived from cyclic β-keto esters and C_2-symmetric pyrrolidines and investigations in this area are continuing.

SYNTHETIC APPROACHES TO HUPERZINE A AND B

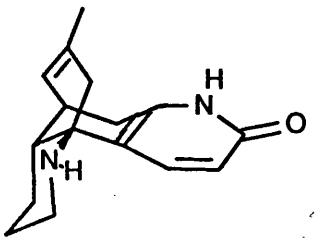
5.1 INTRODUCTION

In 1986, Liu *et al* reported the structures of two new lycopodium alkaloids, huperzine A (62) and huperzine B (63) isolated from *huperzia serrata* (Thumb) Trev, a Chinese folk medicine.[39]



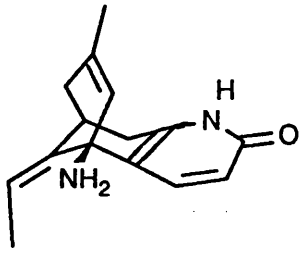
huperzine A

(62)



huperzine B

(63)



selagine

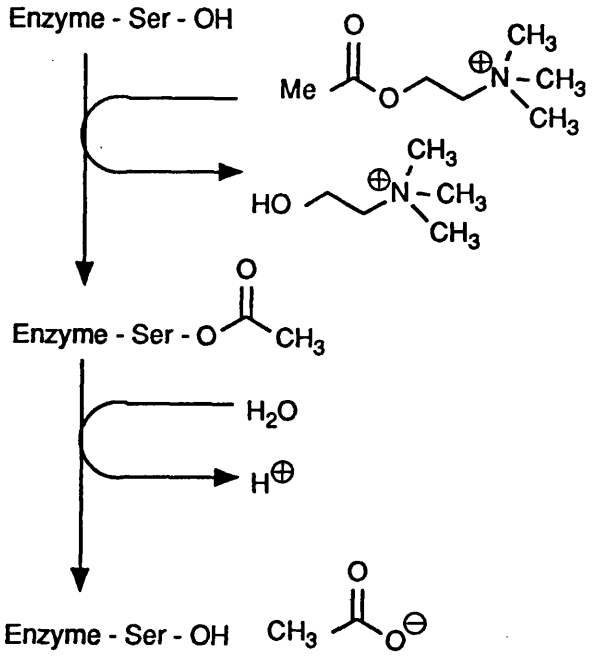
(216)

The structure of a related compound, selagine **(216)**, differing from huperzine A only in the position of the bridge double bond and the geometrical isomerism of the exocyclic olefin, was reported in 1960.[164] However, recent studies have shown that the earlier structural assignments were incorrect and that selagine is identical to huperzine A.[165]

Pharmacologically, huperzine A and B have attracted interest due to their potent anticholinesterase activity which has implications in the development of a treatment for Alzheimers disease.

5.2 ANTICHOLINESTERASE AGENTS

Acetylcholinesterase (AChE) functions in the central and peripheral nervous systems in the transmission of action potentials across nerve-nerve and


Enzyme - Ser - OH
Me
HO
Enzyme - Ser - O
CH_3
H_2O
$H^{\oplus}$
Enzyme - Ser - OH
CH_3

Scheme 145

neuromuscular synapses.[166] When the nerve impulse reaches the end of an axon and depolarizes the membrane, acetylcholine is released and diffuses across the synapse and binds to the acetylcholine receptor in the postsynaptic membrane. This produces a depolarization of the membrane and triggers the action potential in the post synaptic cell. Acetylcholine is hydrolysed by AChE and the polarization of the postsynaptic membrane is restored.

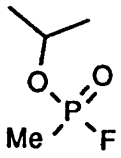
The catalytic mechanism for the hydrolysis of acetylcholine by AChE is shown in Scheme 145.

Acetylcholine reacts with a specific serine residue in the active site of AChE to form a covalent acetyl-enzyme intermediate and choline is released. The acetyl-enzyme complex reacts with water to form acetate and regenerate the enzyme.

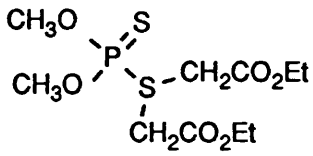
The widespread distribution of cholinergic neurons throughout both the central and peripheral nervous system has made AChE an attractive target for inhibition by both toxic and therapeutic agents.[167]

Chemical warfare nerve gases (eg Sarin **(217)**) are among the most toxic agents ever synthesized. The extreme toxicity of these compounds is due to their irreversible inactivation of AChE. However, related organophosphorus compounds have found widespread use as insecticides (eg malathion **(218)**).

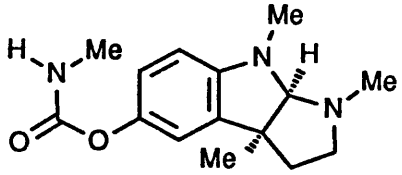
The carbamates, physostigmine **(219)** and neostigmine **(220)** are useful therapeutics agents in the treatment of glaucoma and myasthenia gravis respectively. These compounds are reversible inhibitors of AChE. The mechanism of inhibition involves transient carbamoylation of the active site serine of AChE to give an intermediate complex (Figure 7) which is



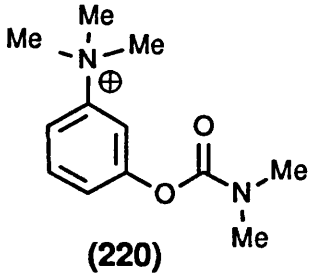
(217)



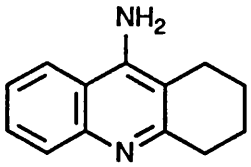
(218)



(219)



(220)



(221)

hydrolysed at a slow rate as compared to the acetyl-enzyme complex shown in Scheme 145.

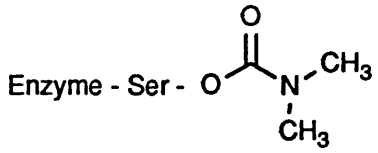
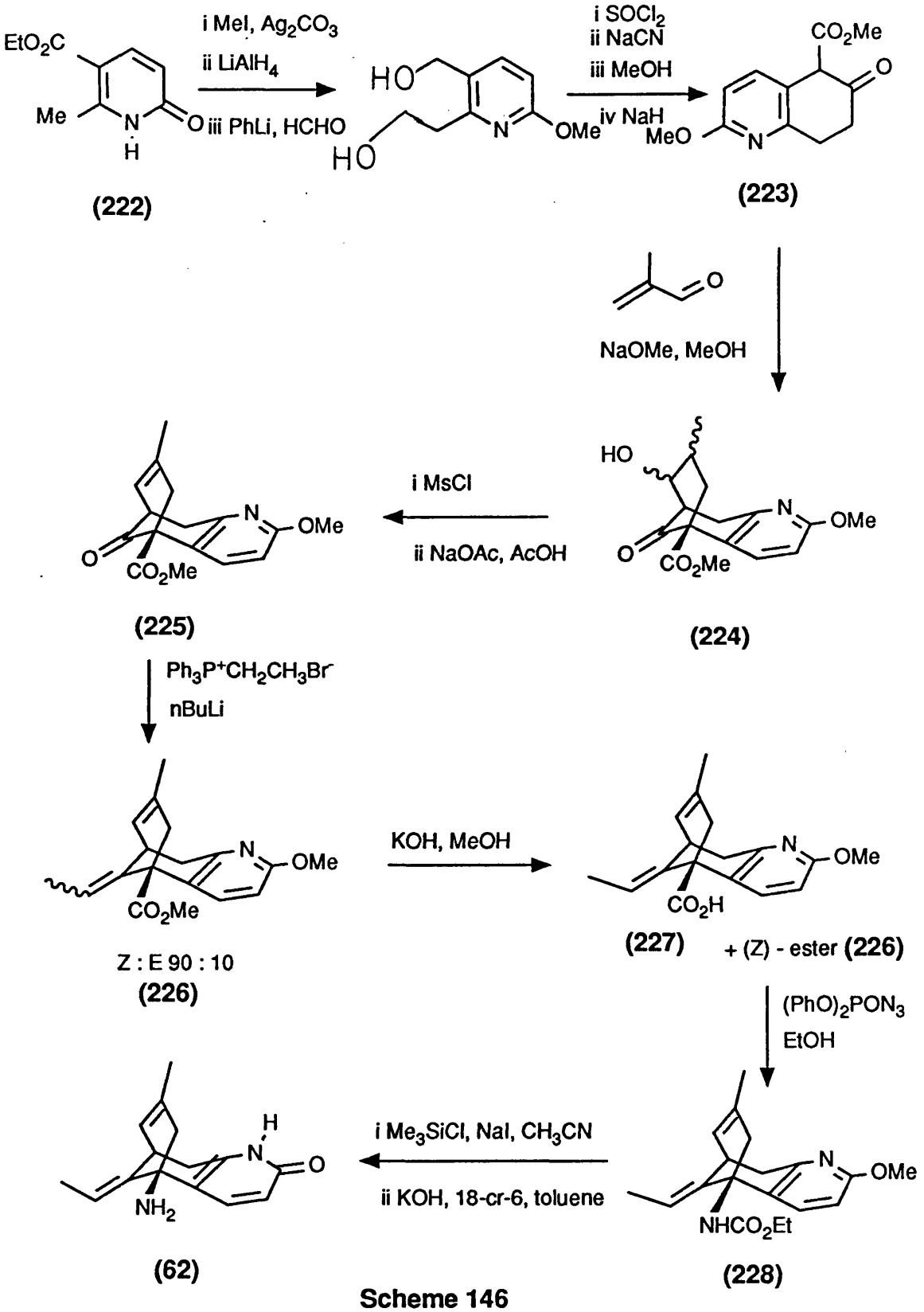


Figure 7

A hallmark of Alzheimer's disease is a developing cholinergic deficit.[168] Reversible inhibitors of AChE that can enter the central nervous system may be useful in allaying the symptoms of senile memory loss by increasing levels of acetylcholine in the brain by inhibition of AChE. In clinical trials, 1,2,3,4-tetrahydro-9-aminoacridine **(221)**, a potent centrally acting acetylcholinesterase, is claimed to improve the memories of elderly Alzheimer's patients.[169] Clinical studies of huperzine A in the treatment of myasthenia gravis and memory impairment in elderly patients both showed promising results.[40] *In vitro* studies have shown that huperzine A is three times more potent than physostigmine as an inhibitor is huperzine A> physostigmine > neostigmine > huperzine B.[170] Also, huperzine A shows less side effects than either physostigmine or tetrahydroacridine **(221)** with long lasting AChE inhibition.[171]

The mechanism of inhibition of AChE by huperzine A is not known but it is suggested that huperzine A acts as an acetylcholine mimic in a different manner to **(219)**. (-)-Huperzine A is over 30 times more active than its enantiomer. This is in contrast to physostigmine where the (+)-isomer is over 700 times less potent than its enantiomer which must reflect the more critical positioning necessary to carbamoylate the enzyme. Huperzine A cannot form a covalent complex with the serine hydroxyl group.[31]

Hence, huperzine A has attracted interest in the search for improve AChE


EtO2C
Me
N
H
O
i MeI, Ag2CO3
ii LiAlH4
iii PhLi, HCHO
HO
HO
N
OMe
i SOCl2
ii NaCN
iii MeOH
iv NaH
MeO
N
CO2Me
O
(222)
(223)
O
NaOMe, MeOH
HO
N
OMe
O
CO2Me
(224)
i MsCl
ii NaOAc, AcOH
N
OMe
O
CO2Me
(225)
Ph3P+CH2CH3Br-
nBuLi
N
OMe
CO2Me
Z : E 90 : 10
(226)
KOH, MeOH
N
OMe
CO2H
(227)
+ (Z) - ester (226)
(PhO)2PON3
EtOH
N
OMe
NHCO2Et
(228)
i Me3SiCl, NaI, CH3CN
ii KOH, 18-cr-6, toluene
H
N
O
NH2
(62)

Scheme 146

inhibitors in the treatment of Alzheimer's disease and this has stimulated synthetic efforts in this area.

5.3 THE SYNTHESIS OF HUPERZINE A

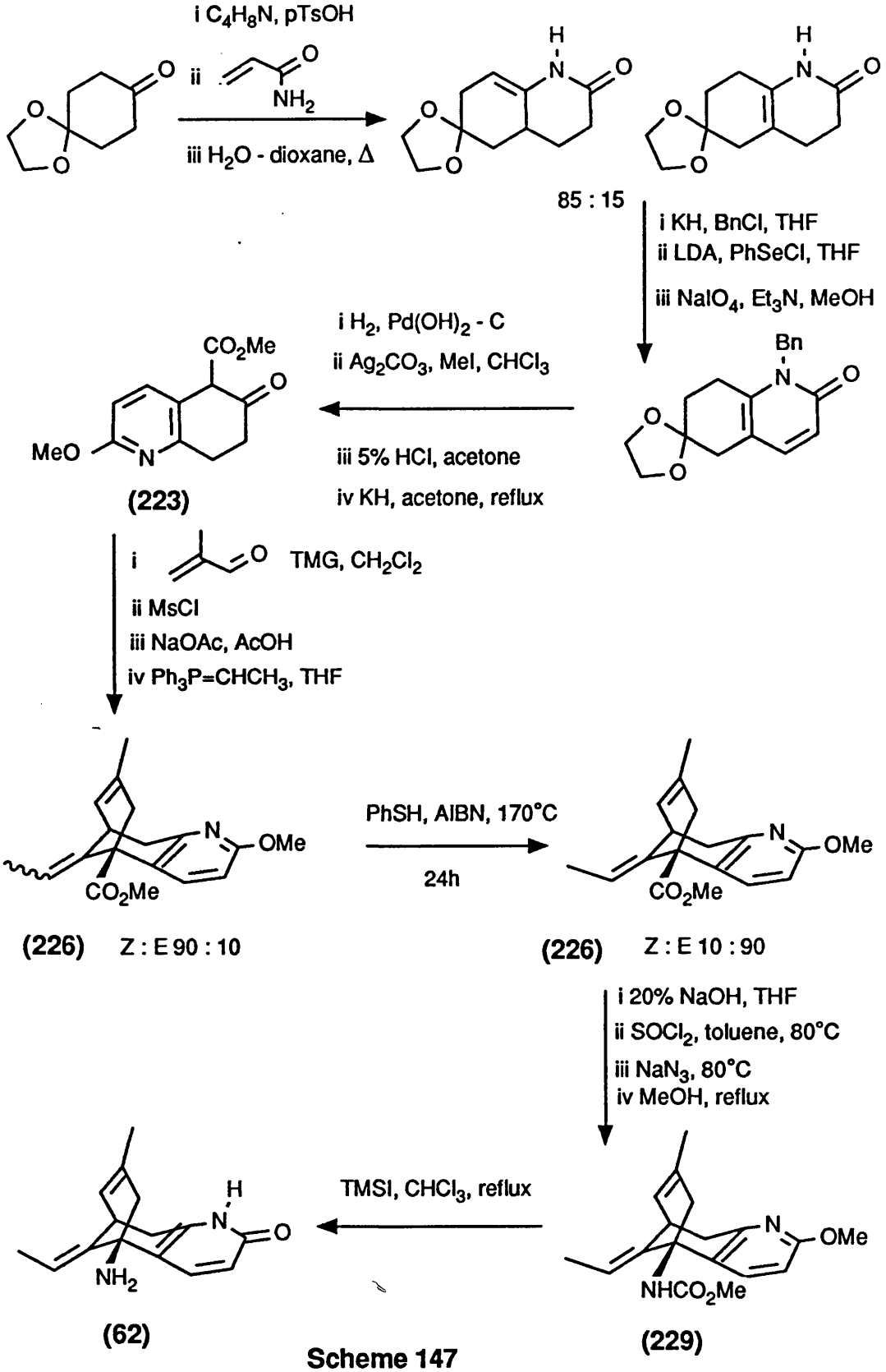
In 1989, two total synthesis of racemic huperzine A were published simultaneously and both adapted a similar strategy. The route of Qian and Ji is shown in Scheme 146.[172]

The β-keto ester **(223)** was prepared from pyridone **(222)** in 39% overall yield. The key bridged intermediate **(225)** was obtained using the method of Raphael.[173] Base catalysed Michael-aldol reaction of β-keto ester **(223)** with methacrolein gave the alcohol **(224)**. Conversion to the mesylate and elimination effected dehydration to introduce the bridge double bond.

Wittig reaction with ethylidenetriphenylphosphorane afforded the olefin **(226)** but with a Z:E ratio of 90:10. Hydrolysis of the mixture provided the acid **(227)** with the desired E-stereochemistry and unreacted Z-olefin **(226)**. A modified Curtius reaction afforded the urethane which on deprotection gave (±)-huperzine A **(62)**.

Kozikowski adopted the same strategy in his synthesis of huperzine A.[41,174] The β-keto ester **(223)** was prepared by annealing a pyridone ring to the monoethylene ketal of 1,4-cyclohexanedione in 30% overall yield. (Scheme 147).

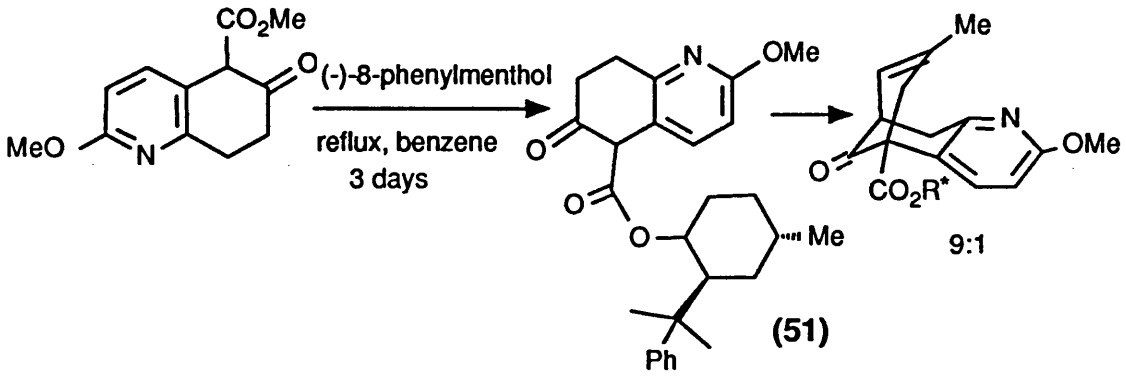
The bridged intermediate **(225)** was prepared using the tandem Michael-aldol-elimination procedure with 1,1,3,3-tetramethylguanidine (TMG) as the catalyst. Wittig reaction gave the olefin **(226)** allowed


i C_4H_8N, pTsOH
ii
iii H_2O - dioxane, Δ
85 : 15
i KH, BnCl, THF
ii LDA, PhSeCl, THF
iii $NaIO_4$, Et_3N, MeOH
i H_2, $Pd(OH)_2$ - C
ii Ag_2CO_3, MeI, $CHCl_3$
iii 5% HCl, acetone
iv KH, acetone, reflux
(223)
i
TMG, CH_2Cl_2
ii MsCl
iii NaOAc, AcOH
iv $Ph_3P{=}CHCH_3$, THF
PhSH, AIBN, 170°C
24h
(226) Z : E 90 : 10
(226) Z : E 10 : 90
i 20% NaOH, THF
ii $SOCl_2$, toluene, 80°C
iii NaN_3, 80°C
iv MeOH, reflux
TMSI, $CHCl_3$, reflux
(62)
(229)

Scheme 147

separation of the isomers. Sequential treatment of the acid (**227**) with thionyl chloride, sodium azide and methanol gave urethane (**229**) and a single deprotection step afforded huperzine A.

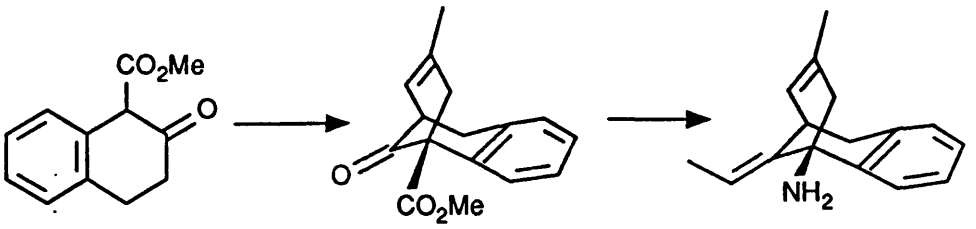
In 1991, Kozikowski reported an asymmetric synthesis of (-)-huperzine A, based on this strategy starting from β-keto ester (**51**) incorporating (-)-8-phenylmenthol as a chiral auxiliary.[31] (Scheme 148).



Scheme 148

When the tandem Michael-aldol reaction was carried out at -20°C, a 9:1 ratio of diastereomers was obtained which, after elimination of water, were separable by chromatography. The major diastereomer was converted to (-)-huperzine A, the naturally occurring enantiomer, and the minor diastereomer to the (+)-enantiomer.

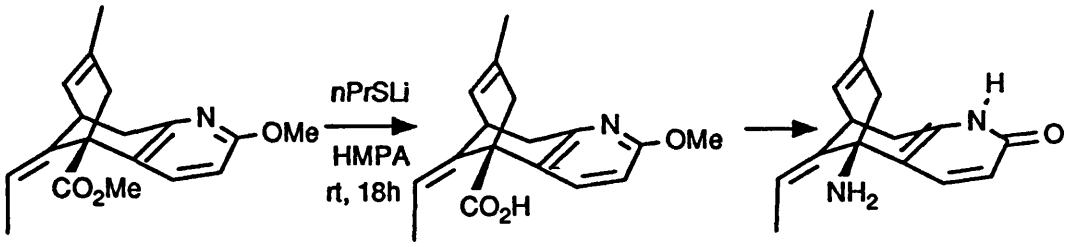
Kozikowski has synthesized a variety of analogous of huperzine A in an attempt to identify the structural requirements for anti AChE activity. The benzenoid analogue (**231**) of huperzine A was prepared by an analogous route starting from tetralone (**230**).[175] (Scheme 149). The benzoanalogue (**231**) was found to be 10^3 times less potent than huperzine A in *in vitro* studies demonstrating the requirement for the pyridone ring for anti AChE activity.



(230) **(231)**

Scheme 149

The analogue (Z)-huperzine A was prepared as its structure might represent a hybrid of the structures of huperzine A and B and might retain the formers activity and the latters improved toxicity profile.[176] (Z)-Huperzine A was prepared from (Z)-olefin **(226)** which was cleaved (lithium n-propylmercaptide in HMPA) to give the acid (Z)-**(227)** which was converted to (Z)-huperzine A. (Scheme 150). Studies showed the activity (Z)-huperzine A to be similar to that of huperzine B.

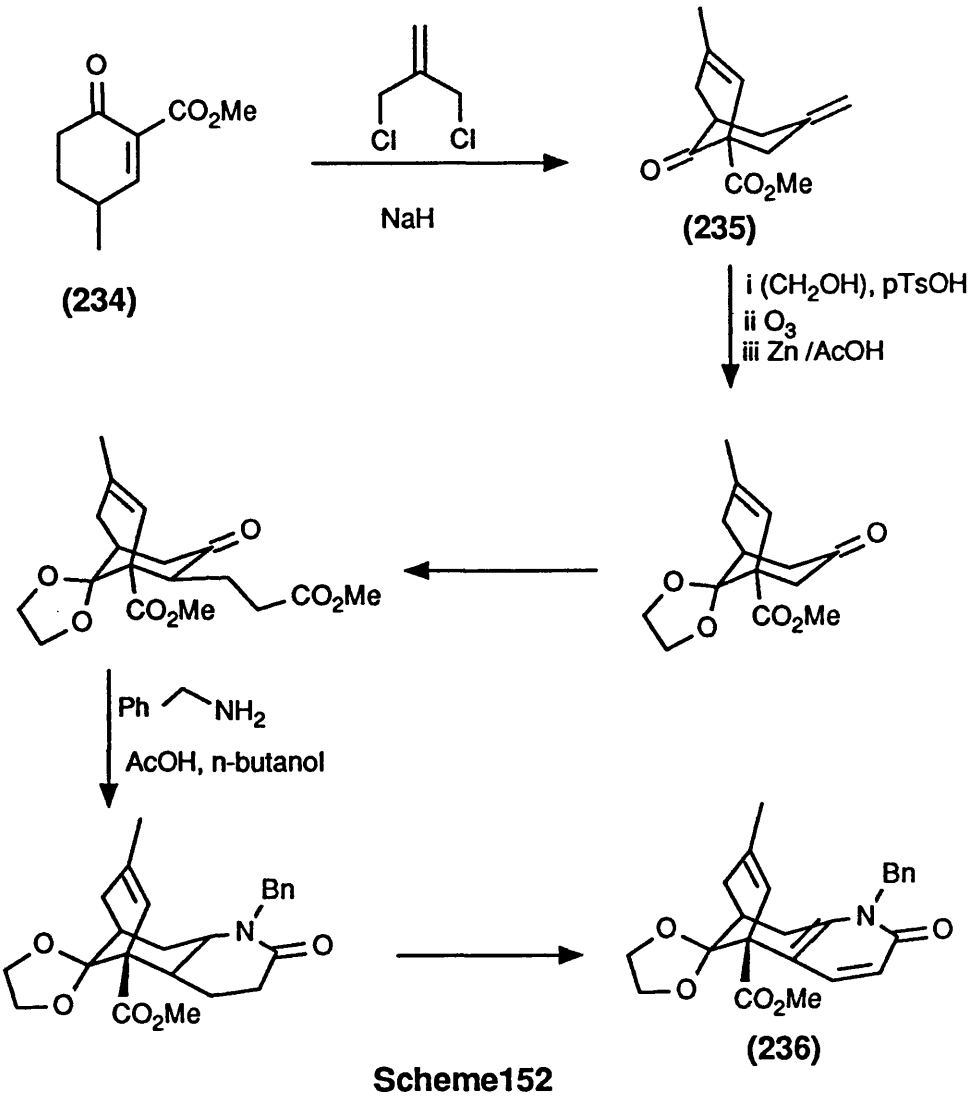


(Z)- (226) **(Z) - (227)** **(Z)- huperzine A**

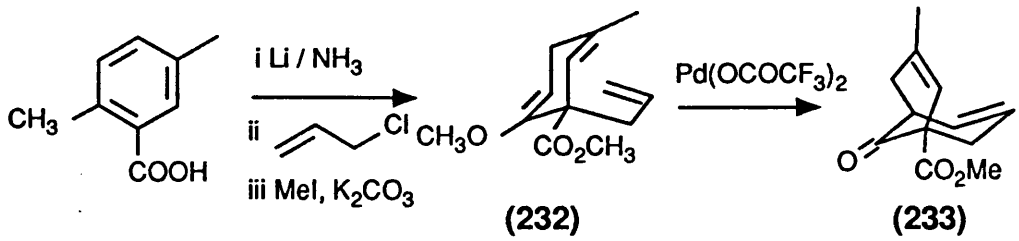
Scheme 150

A variety of analogues containing trivial modifications of the huperzine skeleton have also been prepared but none are as active as huperzine A as inhibitors of AChE.[174]

The total synthesis of selagine **(216)** remains to be achieved but two approaches to the tricyclic skeleton have been reported. Kende has prepared the bicyclononane core **(233)** *via* an intramolecular cyclisation of the triene ester **(232)** mediated by palladium (II) trifluoroacetate.[177] (Scheme 151).


O
CO2Me
Cl
Cl
NaH
(234)
(235)
i (CH2OH), pTsOH
ii O3
iii Zn /AcOH
CO2Me
Ph
NH2
AcOH, n-butanol
Bn
N
(236)

Scheme152



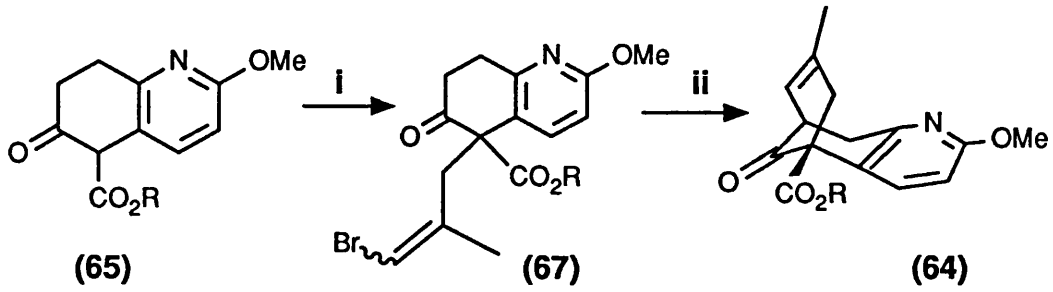
Scheme 151

Gravel has prepared the tricyclic core (**236**) from the αβ unsaturated ester (**234**).[178] Reaction of ester (**234**) with methallyldichloride and sodium hydride provided the bicyclononane skeleton (**235**) and subsequent elaboration of this intermediate gave the tricyclic skeleton (**236**). (Scheme 152).

These two strategies introduce the bridge double bond with the correct regioselectivity for selagine but are not amenable to the synthesis of the huperzine skeleton.

5.4 SYNTHESIS OF THE TRICYCLIC HUPERZINE SKELETON

The asymmetric synthesis of (-)-huperzine A had been the long term goal of the project. Our strategy as outlined in Scheme 153 featured two key steps: (i) the asymmetric alkylation of β-keto ester (**65**) to give an intermediate (**67**) and (ii) an intramolecular cyclisation to give the bridged intermediate (**64**).

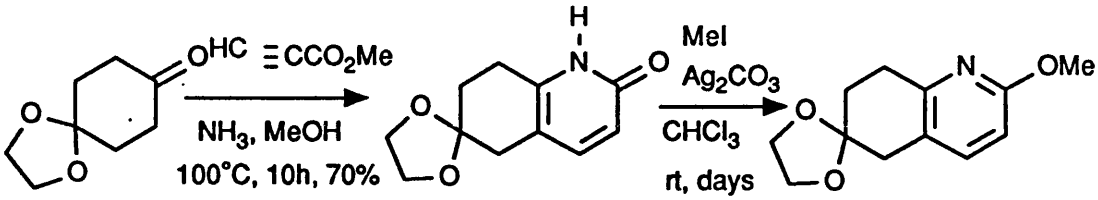


Scheme 153

Although we had not discovered an efficient method for the asymmetric alkylation of β-keto esters, we decided to investigate methods for the

preparation of the intermediate (64) from the racemic β-keto ester.

An improved synthesis of the key intermediate (238) was reported by Kozikowski.[179] (Scheme 154).



(237) (238)

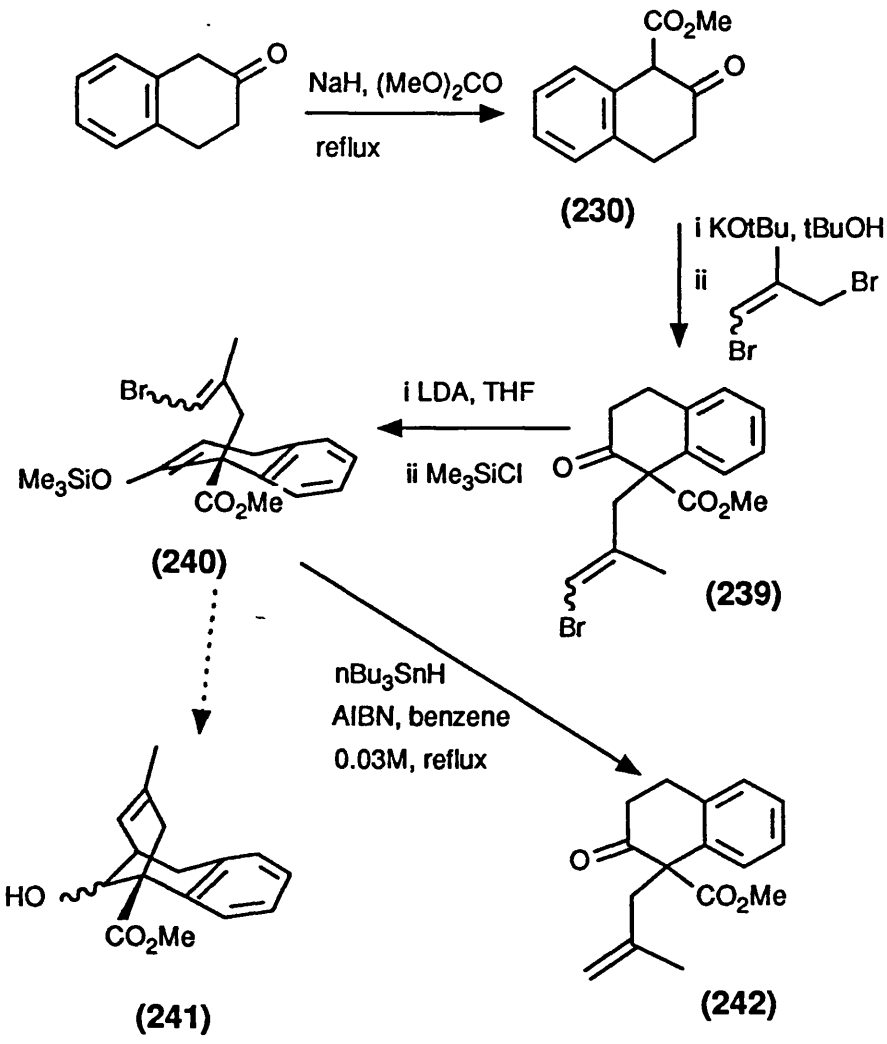
Scheme 154

The monoethylene ketal of 1,4-cyclohexanedione, methyl propiolate and an ammonia saturated solution of methanol were heated in a Parr vessel at 100°C for 10h to give the crystalline pyridone (237) in 70% yield after chromatography.

Our attempts to prepare pyridone (237) by this procedure were not very successful. Under the reported conditions, yields of around 10% could be obtained and using ethyl propiolate and ethanol as solvent gave slightly improved results and a yield around 20%. The major product of the reaction was a fluorescent yellow solid which could not be characterized. Attempts to methylate the pyridone (237) using the conditions of Tieckleman[180] were unsuccessful. After filtering the reaction to removed the silver salts, a black tar was obtained from which none of the desired pyridine (238) could be obtained.

Therefore, this approach to the pyridone ring system was abandoned and we concentrated on the benzenoid analogue as a model system.

The substituted β-keto ester (239) was readily prepared from β-tetralone.

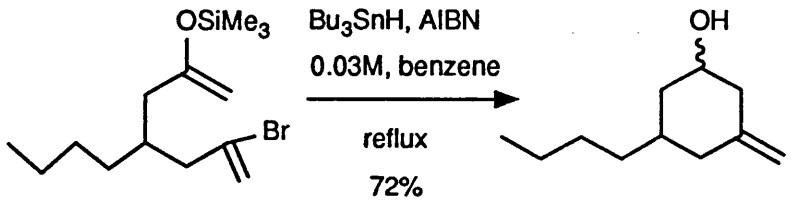

NaH, (MeO)2CO
reflux
CO2Me
O
(230)
i KOtBu, tBuOH
ii
Br
Br
i LDA, THF
ii Me3SiCl
Br
Me3SiO
CO2Me
(240)
(239)
nBu3SnH
AIBN, benzene
0.03M, reflux
HO
CO2Me
(241)
(242)

Scheme 155

Carbomethoxylation of β-tetralone[181] gave β-keto ester (230) in good yield and alkylation with 1,3-dibromo-2-methylpropene (E/Z mixture) gave β-keto ester (239) in 74% yield. (Scheme 155).

Initially, we proposed to introduce the bridge *via* a vinyl radical cyclisation into a silyl enol ether (240) to form the alcohol (241).

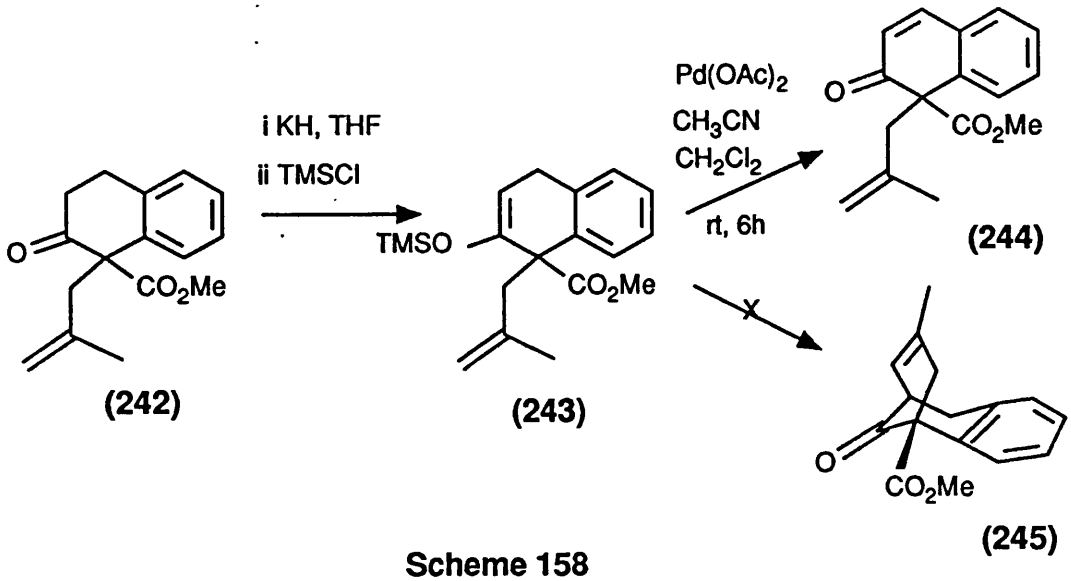
Urabe and Kuwajima had demonstrated that vinyl radicals add to silyl enol ethers to give cycloalkanols.[182] (Scheme 156).



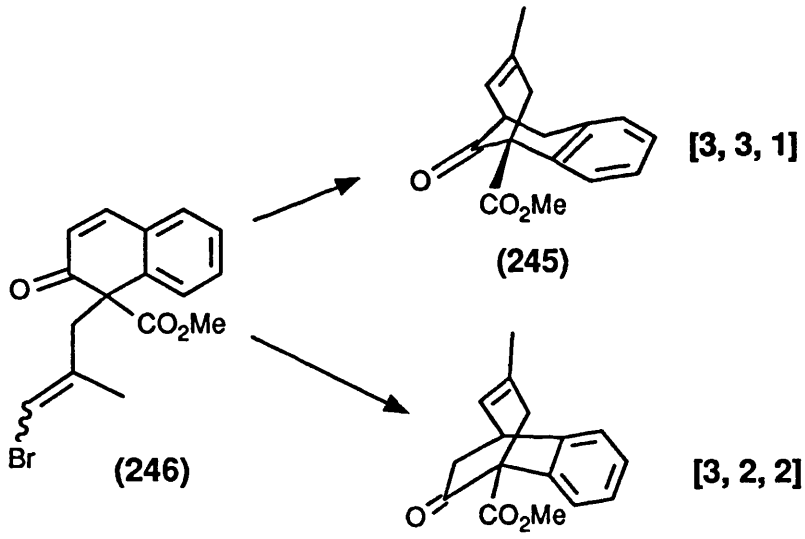
Scheme 156

The silyl enol ether (240) was prepared in 86% yield from β-keto ester (239). Treatment of a 0.03M solution of silyl enol ether (240) in refluxing benzene with tributyl tin hydride and a catalytic amount of AIBN gave the reduced material (242) as the major product and none of the cyclised product (241). (Scheme 155). The product was identified by synthesis of an authentic sample of (242) from the ester (230) and 3-chloro-2-methylpropene.

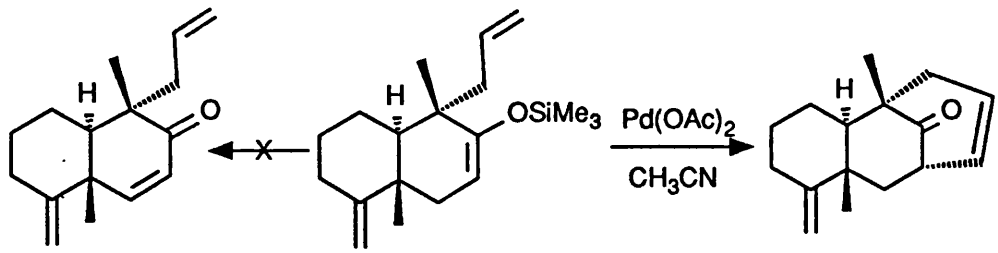
The oxidation of silyl enol ethers with palladium (II) acetate is a valuable method for the preparation of αβ unsaturated compounds,[183] but Kende reported that under the same conditions a facile cyclisation can occur to form bicycloalkenones.[184] (Scheme 157).This reaction was shown to be general for a range of silyl enol ethers of cyclopentanones and cyclohexanones bearing unsaturated side chains.[184,185]



Scheme 158



Scheme 160



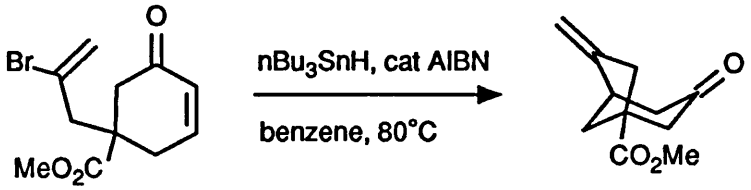
Scheme 157

Therefore, silyl enol ether **(243)**, prepared from β-keto ester **(242)** in 64% yield, was stirred with palladium (II) acetate in acetonitrile-dichloromethane solution under nitrogen for 6h and the sole product formed was the enone **(244)** in low yield.

Under these conditions, none of the cyclised product **(245)** was observed. (Scheme 158).

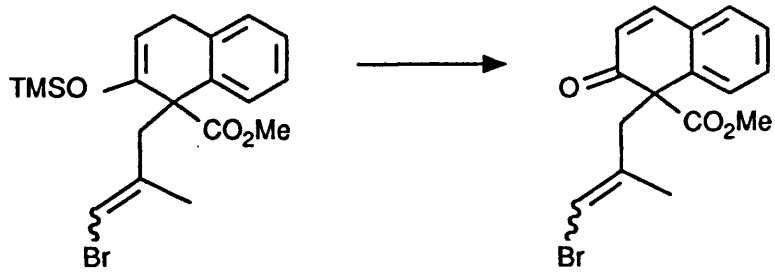
However, this led us to consider an alternative route to compound **(245)** using the enone **(246)** as the substrate for the vinyl radical cyclisation.

Intramolecular addition of vinyl radicals to αβ-unsaturated carbonyl compounds has been demonstrated by Marinovic and Ramanthan,[186] but, in all cases, radical addition occurs at the 4-position of the enone. (Scheme 159).



Scheme 159

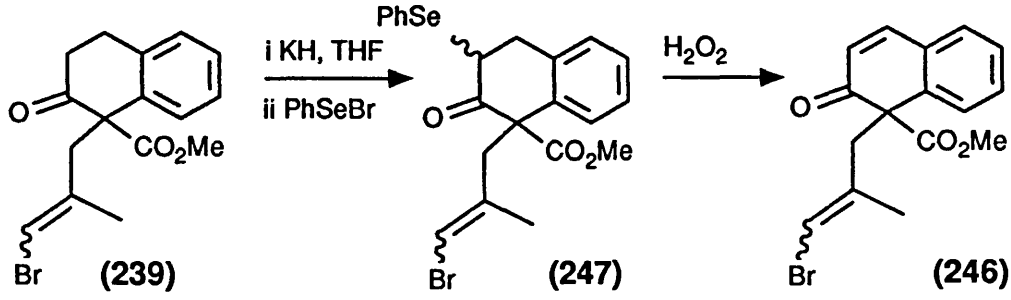
However, cyclisation of the vinyl radical derived from enone **(246)** to the 4-position of the enone would give the [3,2,2]bicyclononene ring system not the desired [3,3,1]bicyclononene **(245)**. (Scheme 160).



(240) **(246)**

conditions	yield
$Pd(OAc)_2$, CH_3CN, CH_2Cl_2	10%
DDQ / collidine	29%
$Ph_3C^+BF_4^-$, CH_2Cl_2	-

Table 15



(239) **(247)** **(246)**

Scheme 161

The regioselectivity of attack of a radical to a 1,2-disubstituted olefin is mainly determined by steric effects, although polar effects can also influence the regioselectivity.[187] However, in the system **(246)** the steric factors are not large and predictions of regiochemistry for radical addition are difficult.

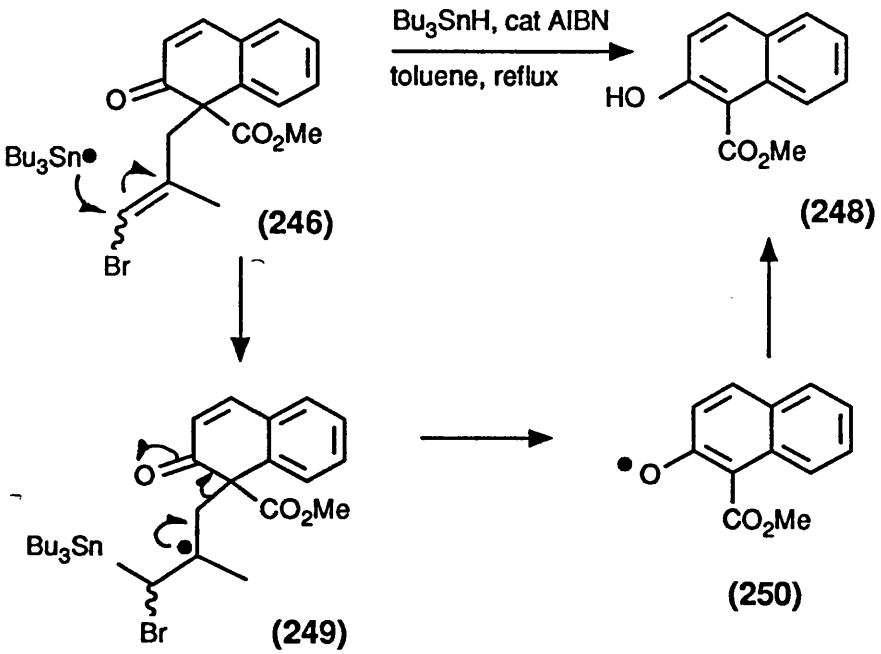
There are a number of methods available for the preparation of enones **(246)** from silyl enol ether **(240)** and the results are shown in Table 15.

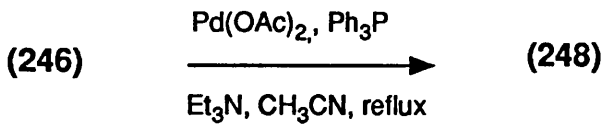
Oxidation of the silyl enol ether **(240)** with palladium (II) acetate using the conditions of Kende,[184] gave the enone **(246)** in low yield (ca 10%). Use of DDQ in the presence of collidine as an oxidising agent,[188] provided the enone in 29% yield after chromatography. Oxidation with trityl fluoroborate[189] provided the enone **(246)** but we were unable to purify **(246)** due to the presence of triphenylmethane.

We found that the method of choice for the preparation of the enone **(246)** was from the β-keto ester **(239)** *via* α-selenylation followed by selenoxide elimination using the one pot procedure of Reich.[190]

The ketone **(239)** was treated with potassium hydride at 0°C followed by addition of phenylselenyl bromide to give the α-selenoketone **(247)**. Selenoxide elimination was effected by addition of hydrogen peroxide solution to the reaction mixture and the enone was isolated in 46% yield after chromatography. (Scheme 161).

The radical cyclisation (Scheme 160) was then attempted using the conditions of Marinovic.[186] A 0.05M solution of enone **(246)** in toluene was heated to reflux and a solution of tributyltin hydride and catalytic AIBN was added slowly. However, no cyclised products were obtained from the reaction. The


Bu3SnH, cat AIBN
toluene, reflux
HO
CO2Me
(248)
O
CO2Me
Bu3Sn
(246)
Br
O
CO2Me
Bu3Sn
Br
(249)
O
CO2Me
(250)


(246)
Pd(OAc)2, Ph3P
Et3N, CH3CN, reflux
(248)

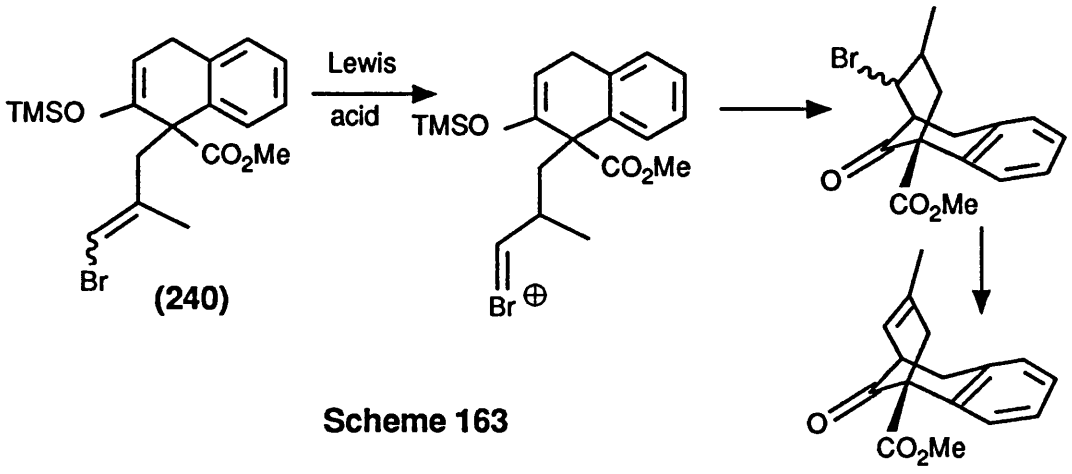
Scheme 162

only product was identified as methyl 2-hydroxy-1-napthalenecarboxylate **(248)** (Scheme 162).

A mechanism for the formation of ester **(248)** can be proposed (Scheme 162). The tributyltin radical adds into the double bond to form an alkyl radical **(249)** rather than abstracting bromine to form the vinyl radical. The radical **(249)** can then fragment to form the stable radical **(250)** containing the aromatic naphthalene ring.

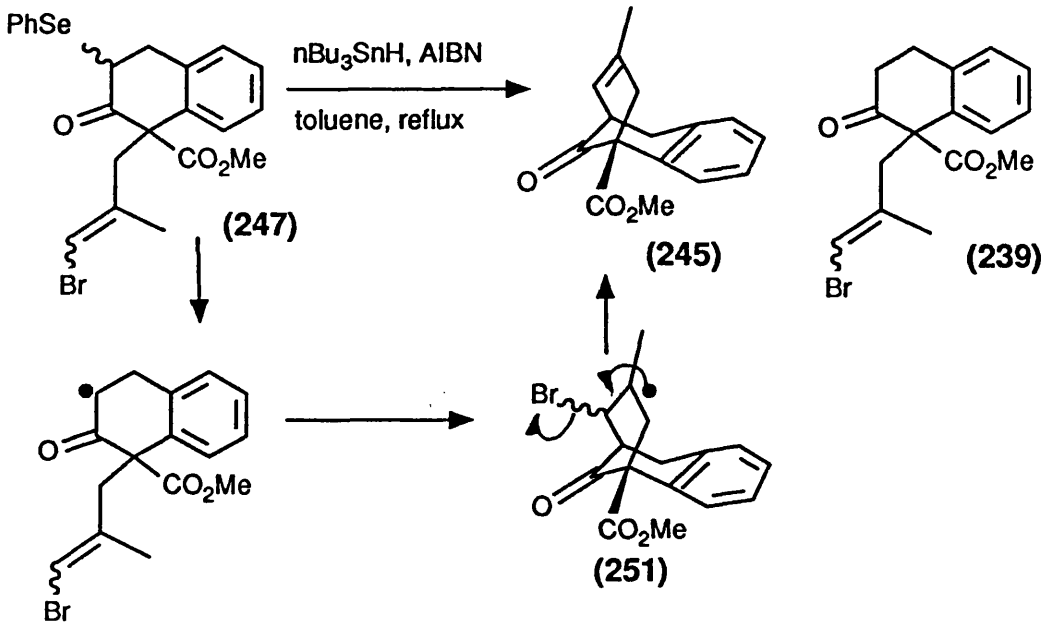
Interestingly, exposure of enone **(246)** to the standard Heck reaction conditions,[191] catalytic palladium (II) acetate, triphenylphosphine, triethylamine in refluxing acetonitrile, yielded the same hydroxynaphthoate ester **(248)** (Scheme 162). The mechanism of this unusual reaction is not known but it is clear that the formation of the aromatic naphthalene system must be the driving force for the reaction.

An alternative strategy based on a Lewis acid catalysed cyclisation of silyl enol ether **(240)** was investigated. (Scheme 163).



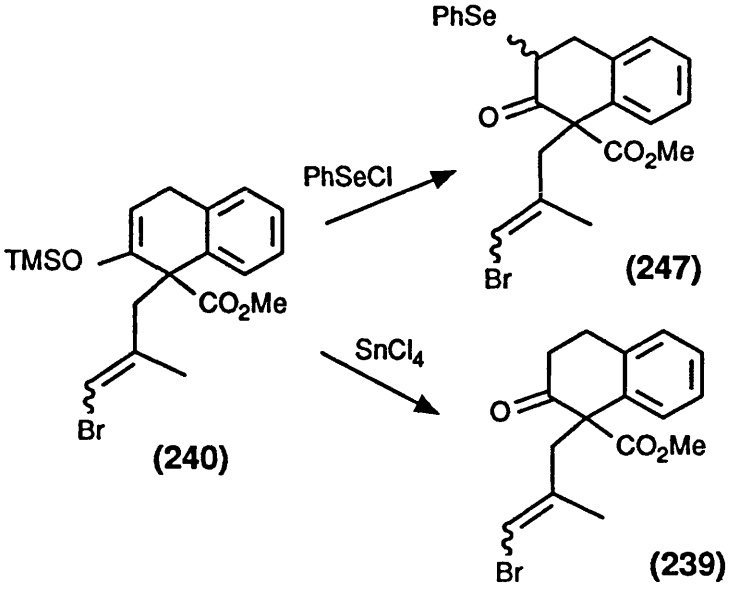
Scheme 163

With a range of Lewis acids ($SnCl_4$, TMSOTf, AgOTf, $ZnBr_2$), the only product formed on treatment of silyl enol ether **(240)** in dichloromethane at -78°C was the β-keto ester **(239)**. However, when a solution of silyl enol ether



Scheme 165

(240) was treated with phenyl selenylchloride at -78°C, α-selenoketone (247) was isolated in 56% yield as a mixture of four diastereomers. (Scheme 164).



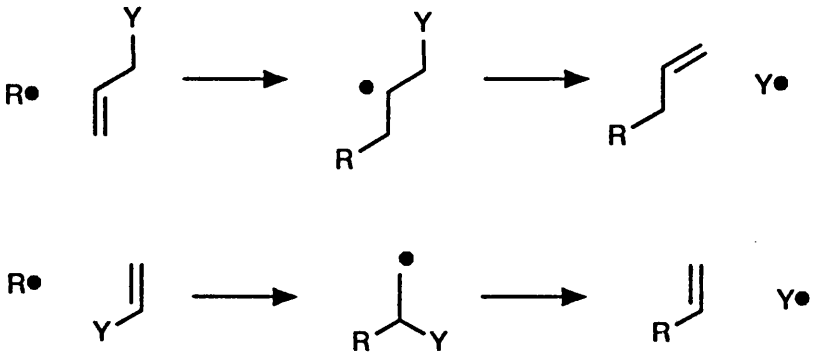
Scheme 164

The α-selenoketone (247) presents an alternative strategy for an intramolecular radical cyclisation to prepare the bridged intermediate (245). An acyl substituted radical can be generated from the selenide (247), which could add to the olefin to form either 5-membered ring or 6-membered ring products.

However, intramolecular cyclisations of acyl-substituted radicals where the carbonyl group is part of the ring, 6-endo ring closure predominates over 5-exo closure.[192]

When a solution of α-selenoketone (247) in refluxing toluene was treated with tributyl tin hydride and catalytic AIBN, the cyclised product (245) and the reduced product (239) were formed as 1:1 mixture. (Scheme 165) The acyl substituted radical adds to the double bond (6-endo) to form the radical (251) which undergoes elimination of bromine radical to form the double bond in the correct regiochemistry for the huperzine skeleton.

This reaction represents a relatively novel example of "the fragmentation method" for radical generation.[193] Addition of a radical to a double bond, followed by rapid fragmentation of a suitable C-Y bond, generating a radical (Y•) which can function as the chain transfer agent are common with appropriately substituted allylic and vinylic compounds. (Scheme 166). The allylic process is much more common than the vinylic process.



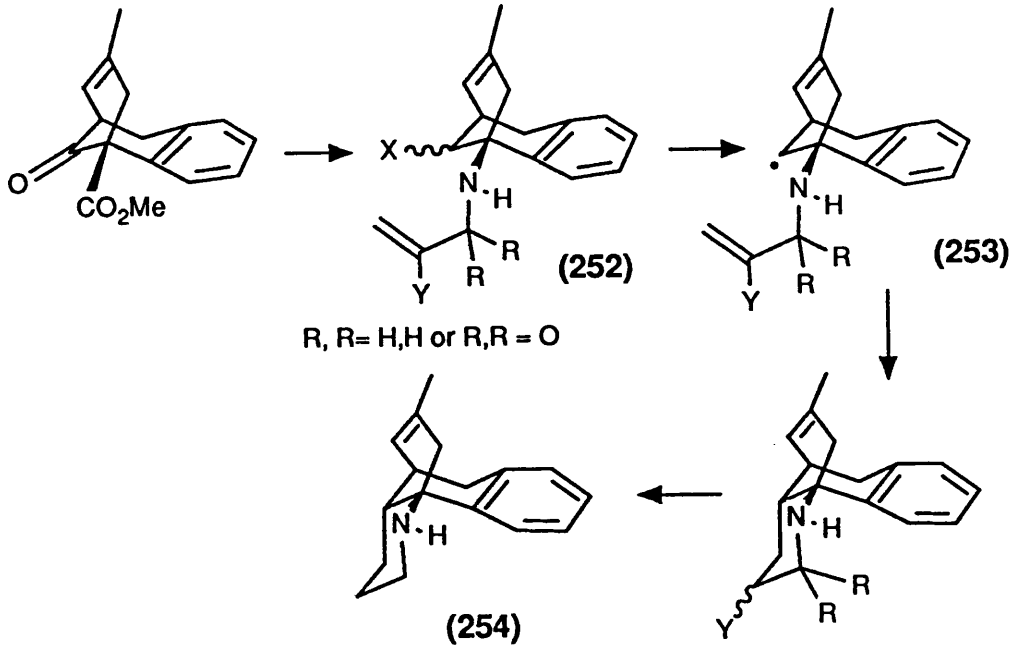
Y = trialkyltin, cobaloxime, thiophenyl

Scheme 166

If the radical(Y•) can act as a chain transfer agent the reaction should be catalytic in tributyltin hydride.

Therefore the α-selenoketone **(247)** was treated with a catalytic amount of tributyltin hydride (10 mol%) but this resulted in only 10% conversion to the cyclised product **(245)** accompanied by 90% unreacted α-selenoketone **(247)** as observed by ^{1}H nmr. The bromine radical cannot act as a chain transfer agent.

In conclusion, the radical cyclisation of the α-selenoketone **(247)** provides access to the bicyclic core of the huperzine skeleton. This method is amenable to an asymmetric synthesis of huperzine A if the asymmetric alkylation step can be achieved. (Scheme 153). However, the overall yield for the



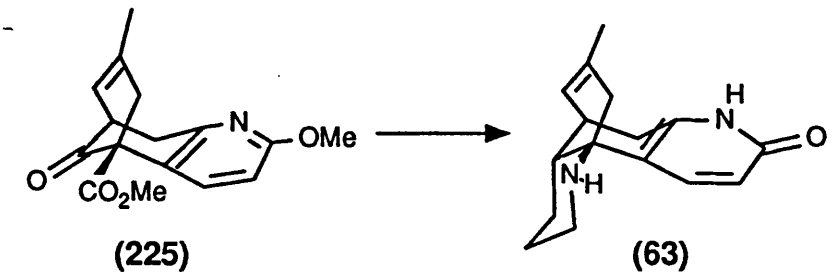
Scheme 168

preparation of the bridged intermediate (245) from the β-keto ester (230) is 13%. This must be compared to Kozikowski's route-tandem Michael-aldol reaction followed by dehydration - which has an overall yield of 40% and is a more practical entry into the huperzine skeleton.

The benzenoid analogue of huperzine A has been prepared from the intermediate (245)[175] (see Scheme 149) in an analogous manner to huperzine A. Therefore, we decided to investigate synthetic approaches to huperzine B which has not been previously synthesized.

5.5 SYNTHETIC APPROACHES TO THE BENZENOID ANALOGUE OF HUPERZINE B

We wanted to investigate the synthesis of huperzine B (63) from the intermediate (225). (Scheme 167).

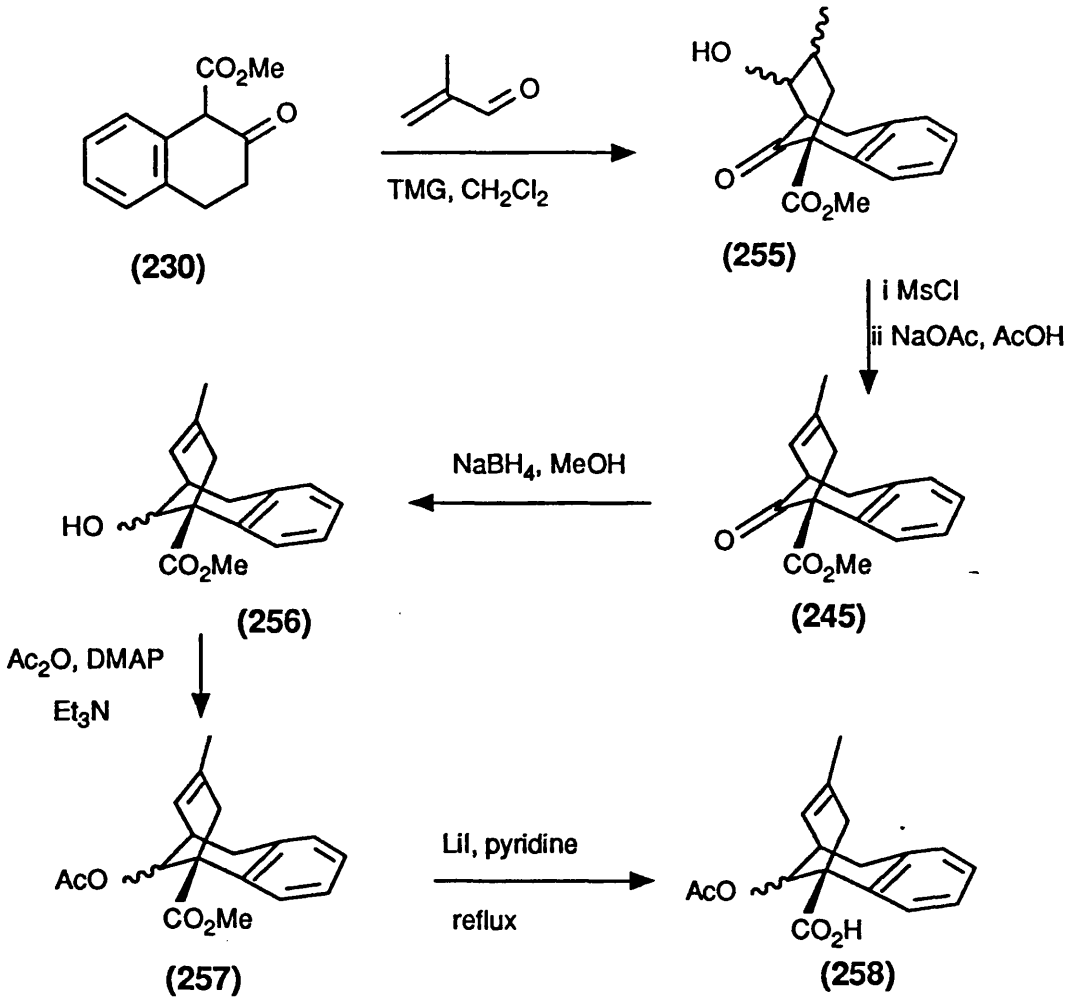


(225) (63)

Scheme 167

Due to the difficulties associated with the preparation of the pyridone ring system, we studied the benzenoid analogue as a model system. A number of strategies can be envisaged for preparing the piperidine ring of huperzine B, however, we decided to concentrate on the radical cyclisation strategy outlined in Scheme 168.

The strategy involved Curtius rearrangement to introduce the bridgehead nitrogen and functionalization to form an allylic amine or amide. (252). The


CO2Me
O
TMG, CH2Cl2
HO
O
CO2Me
(230)
(255)
i MsCl
ii NaOAc, AcOH
NaBH4, MeOH
HO
CO2Me
O
CO2Me
(256)
(245)
Ac2O, DMAP
Et3N
AcO
CO2Me
LiI, pyridine
reflux
AcO
CO2H
(257)
(258)

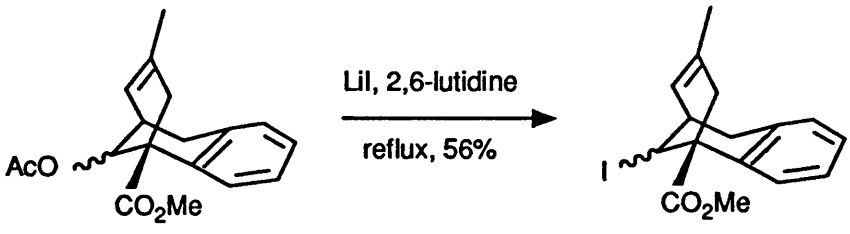
Scheme 169

ketone function would be converted to a group X and cleavage the C-X bond would generate a radical (**253**). We felt that substitution of the olefin with a group Y would favour radical addition at the terminal end of the olefin to form the piperidine ring on both steric and electronic grounds. Subsequent reduction of the amide and removal of the blocking group Y would give the benzenoid analogue of huperzine B (**254**).

The key intermediate (**245**) was prepared on a moderate scale (20 mmol) using Kozikowski's route.[41] β-Keto ester (**230**) was reacted with methacrolein in the presence of 1,1,3,3-tetramethylguanidine as catalyst to yield the alcohol (**255**). Mesylation and elimination by refluxing in glacial acetic acid in the presence of sodium acetate gave the ester (**245**) in 48% yield. (Scheme 169).

Ketone (**245**) was reduced with sodium borohydride to give the alcohol (**256**) as a mixture of diastereomers which was protected as the acetate (**257**). Selective cleavage of the methyl ester of acetate (**257**) was accomplished by a S_N2 type dealkylation.[194] Heating ester (**257**) in pyridine in the presence of lithium iodide under a nitrogen atmosphere for 20h yielded the acid (**258**) in 41% yield (81% based on recovered starting material). (Scheme 169).

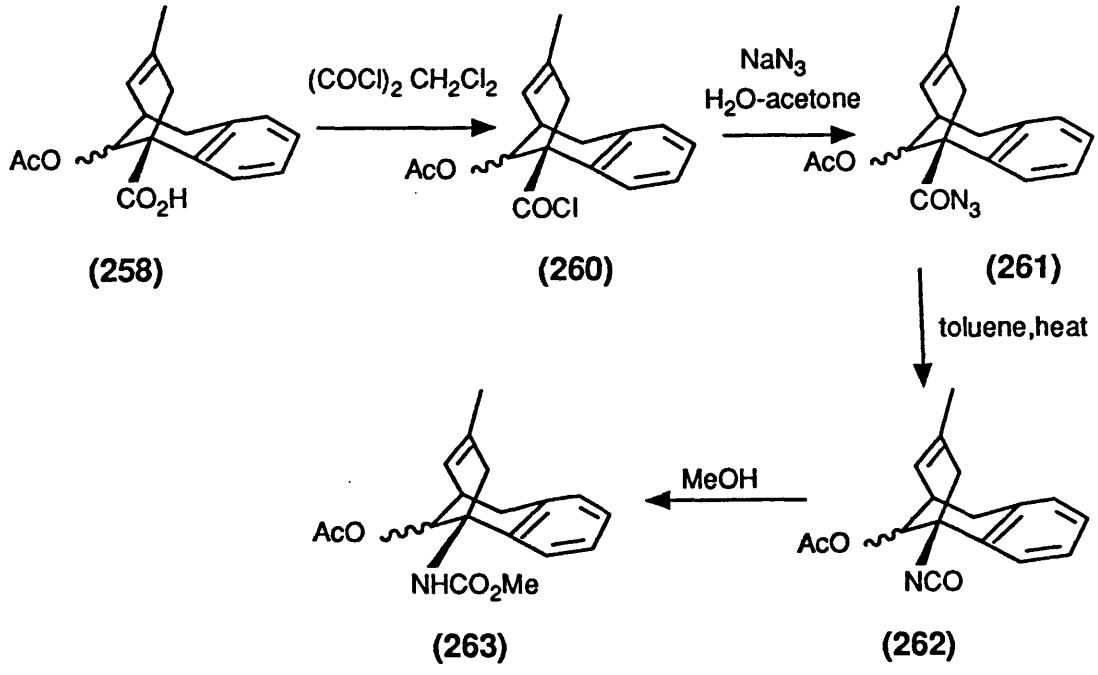
In an attempt to improve the yield of the reaction, the use of refluxing 2,6-lutidine instead of pyridine was examined.



(**257**) (**259**)

Scheme 170

However, in this case, the product of the reaction was not the desired acid



(258) (260) (261) (262) (263)

Scheme 171

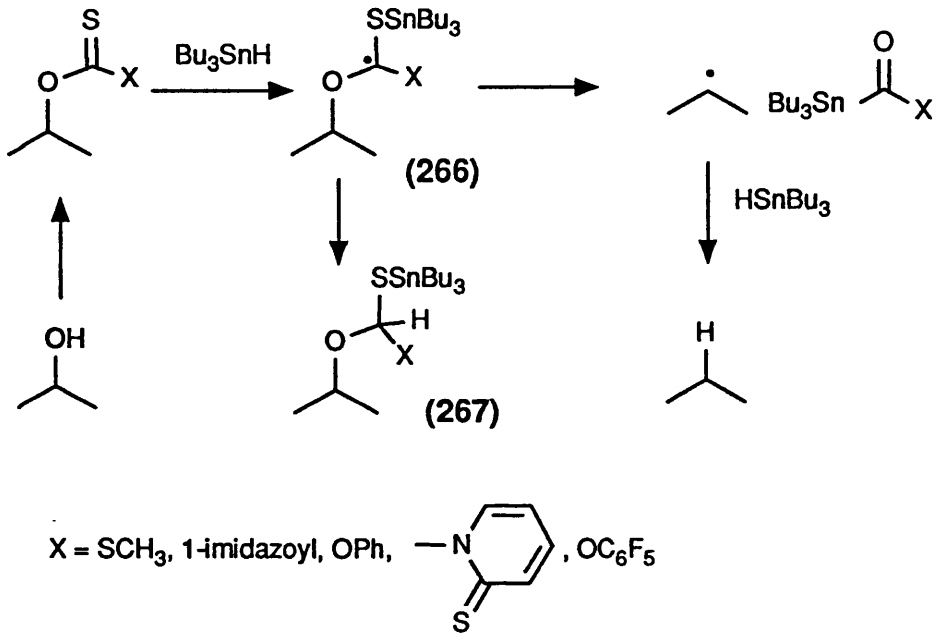
(258) but a compound which was tentatively assigned as the iodoacid (259) (Scheme 170) by the absence of the acetoxy group as shown by ^1H nmr spectrum (δ_C 19.4, -CHI-).

The acid (258) was to be the key intermediate in synthesis of the piperidine ring. Conversion of the acid to the isocyanate (262) followed by trapping with a two carbon unit would give the required intermediate (252) for the radical cyclisation(Scheme 168).

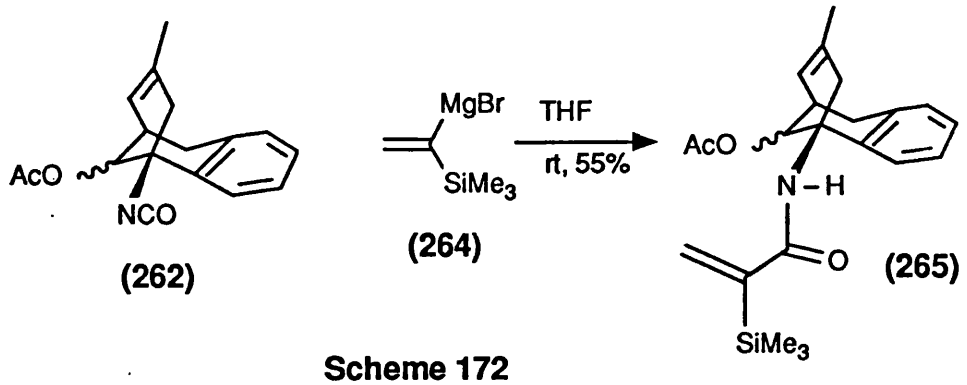
Treatment of the acid (258) with oxalyl chloride gave the acyl chloride (260) in good yield which was not purified but converted to the acyl azide (261) in 94% yield. The acyl azide was isolated as a colourless solid and then heated in refluxing toluene to affect Curtius rearrangement to give the isocyanate (262). (Scheme 171). The isocyanate was trapped as the urethane (263) in an attempt to characterise the isocyanate. The isocyanate was not purified but the isocyanate was quite stable and could be purified by chromatography.

We chose 1-bromovinyltrimethylsilane as our two carbon unit for elaboration of the allyl side chain required for the radical cyclisation precursor, with trimethylsilyl as our blocking group (Y). (Scheme 168). This reagent was prepared from vinylbromide using the procedure of Ganem.[195] The corresponding Grignard reagent (264) was generated from the vinyl bromide and added to isocyanate (262) to give the amide (265) in 55% yield as a mixture of two diastereomers which were separable by chromatography. (Scheme 172).

The radical deoxygenation of secondary alcohol provides a method for the generation of a radical at C-13, as we require for radical cyclisation. Although this method has been widely used to effect deoxygenation, there are only a few


S
X
O
Bu3SnH
SSnBu3
O
X
(266)
Bu3Sn
O
X
HSnBu3
OH
SSnBu3
H
O
X
(267)
H
X = SCH3, 1-imidazoyl, OPh,
N
S
, OC6F5

Scheme 173



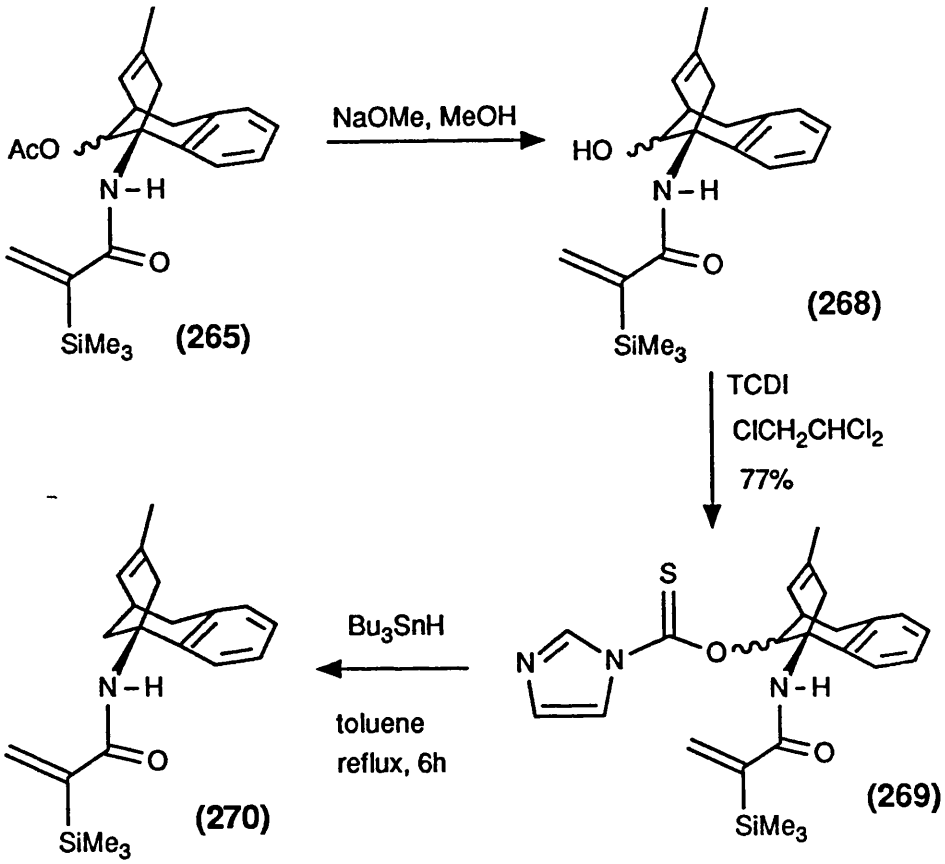
Scheme 172

examples where the intermediate radical has been trapped by groups other than hydrogen.[196] Since the original report by Barton and McCombie[197] a variety of xanthates and thiocarbonates have been used in the reaction.[198] (Scheme 173).

The effect of changing the substituent X is to alter the rate of fragmentation of the intermediate radical **(266)**; pentafluorophenoxy derivatives fragment in minutes. This should reduce the importance of side reactions such as quenching of the radical **(266)** to give the ether **(267)**. We chose the imidazoyl derivative **(269)** as our substrate.

The acetate **(265)** was cleaved (sodium methoxide in methanol) to give the secondary alcohol **(268)** which was converted to the thioester **(269)** by heating with the commercially available thiocarbonyldiimidazole. (Scheme 174).

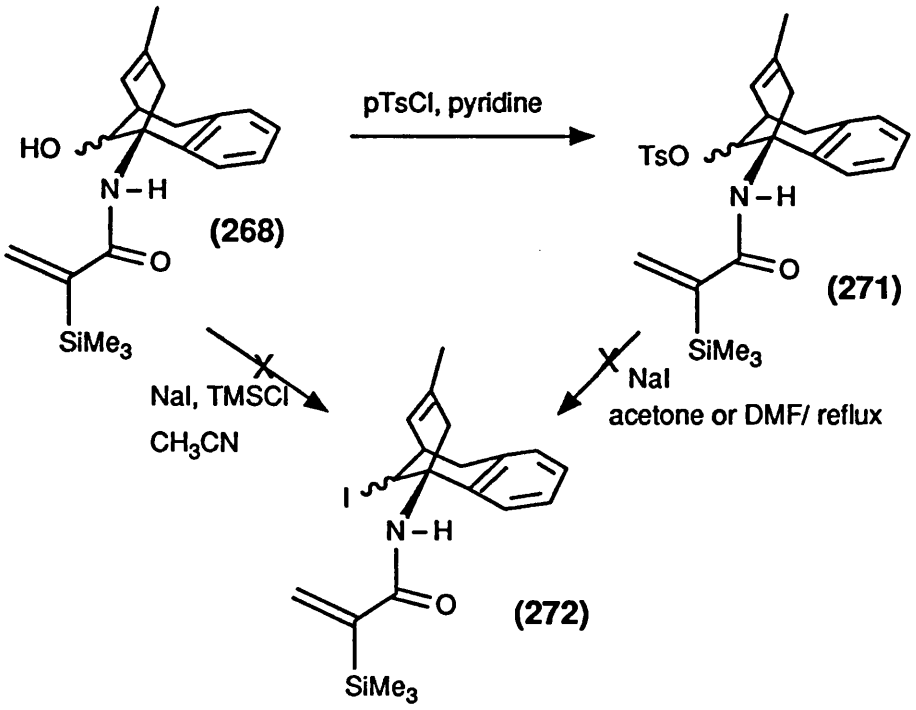
A 0.05M solution of amide **(269)** was heated to reflux in toluene and tributyl tin hydride was added with catalytic AIBN by syringe pump over 2h. After 6h, the solvent was removed under reduced pressure and the residue was purified by chromatography. Starting material **(269)** was recovered (50%) and a product was isolated which was tentatively assigned as the deoxygenated product **(270)** (Scheme 168). The ^{1}H nmr spectrum of this product showed the characteristic pattern of vinyl protons (δ_H 6.0, 1H, d, *J* 2 Hz; 5.5 1H, d, *J* 2 Hz; 5.76, 1H, br s, (-NH); 5.2, 1H, br d) indicating that cyclisation had not


AcO
N-H
O
SiMe3
(265)
NaOMe, MeOH
HO
N-H
O
SiMe3
(268)
TCDI
ClCH2CHCl2
77%
S
N
N
O
N-H
O
SiMe3
(269)
Bu3SnH
toluene
reflux, 6h
N-H
O
SiMe3
(270)

Scheme 174

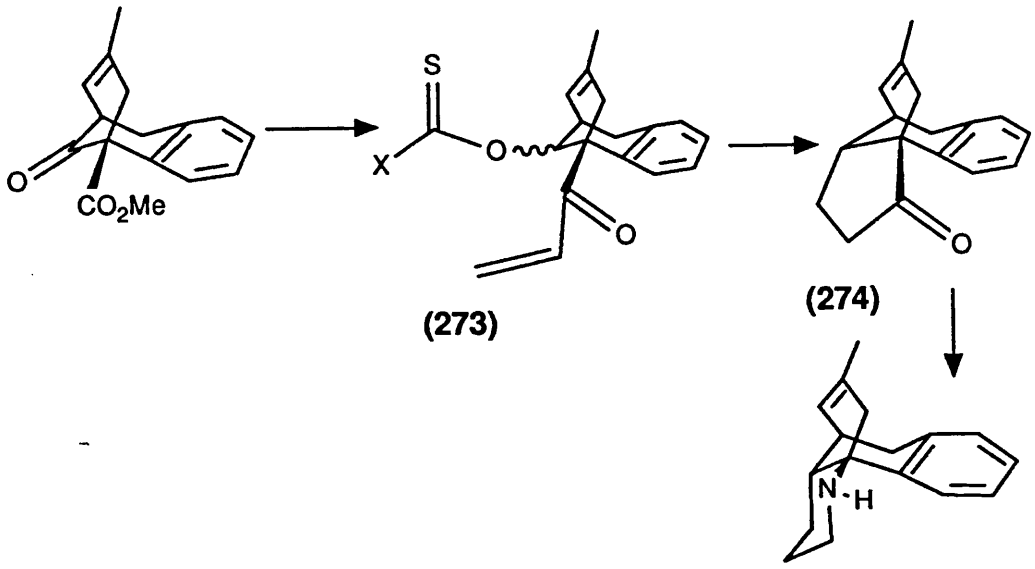
occurred but the characteristic imidazoyl protons had disappeared. However, the tin residues could not be removed from the product to allow complete characterization.

Ideally, other thiocarbonyl compounds would have been screened to discover if the piperidine ring could be formed by this radical cyclisation. However, time did not allow this and instead, we attempted to prepare the iodide **(272)** from which we could generate the radical **(253)**. The alcohol **(268)** was converted to the tosylate **(271)** under standard conditions but all attempts to displace the tosylate failed. (Scheme 175). Attempted conversion of the alcohol **(268)** to the iodide **(272)** using the iodotrimethylsilane method of Olah[199] also failed. (Scheme 175).



Scheme 175

Displacement reactions at C-13 should be possible as illustrated by the formation of the iodoacid **(259)** and further investigation might have solved this problem.



(273)

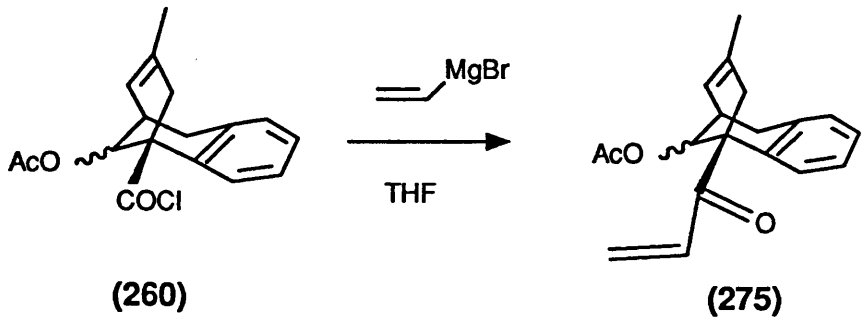
(274)

Scheme 176

An alternative strategy for the preparation of the piperidine ring is based on a Beckmann rearrangement of ketone (**274**). We had envisaged preparing (**274**) *via* an intramolecular radical cyclisation of enone (**273**). (Scheme 176)

It is generally accepted that ketones cannot readily be prepared by the addition of Grignard reagents to acyl chlorides due to the propensity for Grignard reagent to add to the ketone to give the tertiary alcohol as the major product. However, Sato and coworkers have shown that ketones can be prepared from acyl chlorides by reaction with Grignard reagents at low temperatures.[200]

Therefore, we attempted to prepare the enone (**275**) by addition of vinyl magnesium bromide to acyl chloride (**260**). (Scheme177). However, to our surprise, no reaction occurred and the acyl chloride was recovered after chromatography.



(**260**) (**275**)

Scheme 177

The vinylmagnesiumbromide was shown to be good by quantitative addition to benzaldehyde The bulky tricyclic ring system of the acyl chloride (**260**) must prevent reaction at the carbonyl group, except with very reactive nucleophiles such as azide. In view of the failure of this Grignard reaction, this strategy was abandoned.

In conclusion, model studies on the benzenoid analogues of huperzine A and huperzine B have provided a strategy for the preparation of the key β-keto ester intermediate **(245)** by an alkylation-radical cyclisation route. The synthesis of the benzenoid analogue of huperzine B was not completed but further investigations might provide a route to the formation of the piperidine ring *via* a radical cyclisation strategy.

6. EXPERIMENTAL

INSTRUMENTATION AND EXPERIMENTAL TECHNIQUES

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Perkin-Elmer 1310 grating spectrophotometer and peaks are reported (υ_{max}) in wavenumbers (cm^{-1}) with reference to the polystyrene 1028cm^{-1} peak. The abbreviation "br" is appended to a peak to indicate significant broadening. Spectra of liquid samples were taken as thin films on sodium chloride plates, or as solution in chloroform.

Routine mass spectra were obtained in the electron impact mode (E.I.) with an ionising potential of 70eV and in the chemical ionisation mode (C.I.) with *iso*-butane as the reagent gas. These along with high resolution mass determinations in the E.I. mode were recorded with a VG Analytical 7070E instrument and a VG2000 data system. Where possible a molecular ion is indicated along with all sizeable fragments. Where a molecular ion was not observed, a high resolution accurate mass determination in the E.I. mode was carried out on a fragment ion.

Proton magnetic resonance (proton NMR) spectra were recorded at 60MHz on Hitachi Perkin-Elmer high resolution R-23B and Varian Anaspect EM-360 spectrometers, at 270MHz on a Jeol GNM GX FT 270 spectrometer and at 400MHz on a Jeol GNM GX FT 400 spectrometer. Carbon 13 magnetic resonance (^{13}C NMR) spectra were recorded on a Jeol GNM GX FT 270 spectrometer operating at 68MHz and using 90 and 135 DEPT pulse sequences to aid in multiplicity determination. Proton and ^{13}C NMR spectra are expressed in parts per million (δ) downfield from internal tetramethylsilane. Multiplicities are given as follows: singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m), and in ^{13}C NMR spectra quaternary carbons are denoted (q), tertiary carbons (t) , secondary carbons (s), and

primary carbons (p). The abbreviation "br" is appended to a multiplicity to indicate significant broadening.

Melting points (m.p.) were determined on commercially available apparatus (Gallenkamp) and are uncorrected. Elemental microanalysis were carried out using a Carlo Erba 1106 Elemental Analyser. Optical rotations were measured using a Perkin-Elmer 141 polarimeter with concentration (*c*) expressed in g/100ml.

An AI model 93 gas chromatograph with a 0.2mm x 25m OV-1 capillary column and flame ionization detector using helium as carrier gas operating over a temperature gradient (50-150°C) was used for g.c. analyses.

Thin layer chromatography (T.L.C.) was used extensively as a qualitative guide during reactions and for assessing the purity of compounds. Merck DC-alufolien Kieselgel 60 F_{254} containing fluorescent indicator were used for this purpose. Visualisation of reaction components was achieved by illumination under short wavelength (254nm) or using a reagent which would give a colour change with the functional groups present, as described in "Dyeing Reagents for Thin Layer and Paper Chromatography", E. Merck, Darmstadt, 1980.

Unless otherwise stated, petrol refers to that fraction of petroleum spirit boiling in the range 60-80°C. Solvents used as eluants in chromatography were dried and distilled prior to use.

Medium pressure flash chromatography was routinely employed using Kieselgel 60 (Merck 9385) (flash) and 60H silica gel (Merck 7736) for reaction component separations. A pressure gradient was developed using

small, commercially available hand bellows (Gallenkamp). In all cases columns were prepared in the least polar solvent of the eluant mixture and chromatography was carried out with the least polar solvent as initial eluant, then eluting with solvent mixtures of steadily increasing polarity. Material to be chromatographed was pre-adsorbed onto the column support and applied as a thin layer to the top of the column.

Tetrahydrofuran (THF) was pre-dried over sodium wire, then refluxed over sodium benzophenone ketyl under dry nitrogen until anhydrous. This was redistilled immediately prior to use.

Glassware used for water sensitive reactions was baked in an oven at 120°C for approximately 12h and allowed to cool in a desiccator over $CaCl_2$. Flasks and stirrer bars were, however, additionally flame dried under a stream of dry nitrogen. In all experiments the excess solvent was removed with a Büchi rotary evaporator using a water aspirator at room temperature to avoid unnecessary decomposition. All yields quoted are of purified products and are uncorrected unless otherwise stated.

All other reagents and solvents were purified and dried when required using the methods described in D.D. Perrin, W.L.F. Armarego, and D.R. Perrin, "Purification of Laboratory Chemicals", 2nd Edn., Pergamon Press, Oxford, 1980.

Lithium diisopropylamide (LDA) was generated using a standard procedure. *n*-Butyllithium (1 equiv, [1.6M in hexanes]) was added to a solution of diisopropylamine (1 equiv) in THF under a nitrogen atmosphere at 0°C and stirred for 0.5h.

General procedure (A) for alkylation using sodium hydride as a base

A solution of β-keto ester **(78)** (1 equiv) was added to a suspension of sodium hydride (1.1 equiv) in solvent at room temperature under nitrogen and stirred for 0.5h. The solution was cooled to -78°C and alkyl halide (2-5 equiv) was added, the mixture stirred for 1h and allowed to warm to room temperature with stirring for 5h. Water was added and the mixture extracted with ether. Drying ($MgSO_4$) and removal of solvent under reduced pressure yielded an oil which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent.

General procedure (B) for alkylation using LDA as a base

A solution of LDA (1.1 equiv) in THF was cooled to -78°C and a solution of β-keto ester **(78)** (1 equiv) in THF was added slowly. After 0.5h, alkyl halide (2-5 equiv) was added and the solution maintained at -78°C for 1h, then allowed to warm to room temperature for a further 5h. Water was added and the mixture extracted into ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield the product which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent.

General procedure (C) for alkylation using LDA as a base and DMPU as cosolvent

A solution of LDA (1.1 mmol) in THF (1 ml) was cooled to -78°C. DMPU (1 ml) was added dropwise with efficient stirring. β-Keto ester **(78)** (0.3 g, 1 mmol) in THF (1 ml) was added slowly. After 0.5h, alkyl halide (2 mmol) was added and the solution maintained at -78°C for 1h, then allowed to warm

to room temperature for 4h. Work up as procedure B.

General procedure (D) for alkylation using potassium t-butoxide as base

A solution of β-keto ester in t-butanol was added to a suspension of potassium t-butoxide (1.1 equiv) in t-butanol and the mixture warmed to 40°C for 0.5h. Alkyl halide (2-5 equiv) was added and the solution heated slowly to reflux for 4h. After cooling, the mixture was diluted with water and extracted with ethyl acetate. The organic extracts were washed with brine, dried ($MgSO_4$) and solvent removed under reduced pressure to yield the product which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent.

General procedure (E) for alkylation of β-keto ester enamines

The β-keto ester enamine[80] in THF was added dropwise to a solution of LDA (1.1 equiv) in THF at -78°C and the solution stirred for 1h. Alkyl halide (2-5 equiv) was added and after 0.5h, the solution was allowed to warm to room temperature and stirred until the reaction was judged to be complete by g.c. 2M HCl was added and the mixture stirred vigorously overnight to effect hydrolysis. Ethyl acetate was added to the mixture and the layers seperated. The aqueous phase was washed with ethyl acetate and the combined organic phases were washed with saturated aq. $NaHCO_3$ and brine. Drying ($MgSO_4$) and removal of solvent under reduced pressure yielded an oil. The crude reaction mixtures were analysed by nmr and g.c.. Purification by flash column chromatography on silica gel with ethyl acetate/petrol as eluent yielded the product as an oil.

General procedure (F) for alkylation of β-keto ester enamines

A solution of LDA (1.1 mmol) in THF (2 ml) was cooled to -78°C. DMPU (2 ml) was added to the solution which was stirred vigorously. The enamine (1 mmol) in THF (2 ml) was added to the solution and stirred for 1h. Alkyl halide (2-5 mmol) was added and after 1h, the mixture was allowed to warm to room temperature and stirred until the reaction was judged complete by g.c. 2M HCl (5 ml) was added and the mixture stirred overnight. Work up proceeded as procedure E.

General procedure (G) for alkylation of β-keto ester using sodium ethoxide as a base

Sodium metal (1.2 equiv) was added to absolute ethanol. When the metal had dissolved, ethyl 2-oxocyclohexanecarboxylate (1 equiv) in absolute ethanol was added and the mixture stirred for 0.5h. Alkyl halide (2 equiv) was added and the mixture heated to reflux for 3h. After cooling, the reaction was diluted with water and extracted with ethyl acetate (3 times). Drying ($MgSO_4$) and removal of solvent under reduced pressure gave an oil which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent yielding the β-keto ester as an oil.

General procedure (H) for alkylation for chiral enamine (**215**)[5]

n-Butyllithium (1.1 equiv, 1.6M in hexane) was added to a solution of diisopropylamine (1.1 equiv) in dry toluene at 0°C and stirred for 0.5h. The mixture was cooled to -78°C and a solution of enamine (**215**) (1 equiv) in dry toluene was added dropwise to give a red solution which was stirred for a further 0.75h. The cosolvent (2 equiv) was added and the solution stirred for

1h. The solution was allowed to warm to -55°C and alkyl halide (2-5 equiv) was added and stirred and allowed to warm to room temperature for 4h. 10% Citric acid (20 ml) was added and the mixture stirred vigorously for 2h. The layers were separated and the aqueous phase washed with ether (3 times). The combined organic phase were washed with saturated $NaHCO_3$ (aq) and dried ($MgSO_4$) and the solvent removed under reduced pressure to give an oil which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent.

General procedure for preparation of β-keto esters via transesterification[59]

1-Chloro-3-hydroxytetrabutyldistannoxane[61] (10 mol%) was added to a solution of alcohol (1 equiv) and ethyl 2-cyclohexanonecarboxylate (5 equiv) in toluene and the reaction was heated to reflux for 24h. After cooling, solvent was removed under reduced pressure and excess ester was removed by bulb-to-bulb distillation (20°C/0.05 mmHg) to yield the crude β-keto ester.

trans-2'-Phenylcyclohexyl 2-oxocyclohexanecarboxylate **(78)**

The title compound was prepared from *trans*-phenylcyclohexanol **(73)**[55]. Chromatography on silica gel yielded the *ester* **(78)** as a colourless oil (72%), b.p. (bulb to bulb) 220°C (0.05 mmHg) (Found : C, 76.0; H, 8.16. $C_{19}H_{24}O_3$ requires C, 76.0; H, 8.05%); υ_{max} ($CHCl_3$)/cm^{-1} 3980, 1720, 1630, 1600; δ_H (270 MHz, $CDCl_3$) 12.0 (0.5H, s, enol OH), 7.3-7.0 (5H, m, ArH) 4.95 (1H, m -CH-O-), 3.0 (0.5H, m, -COCHCO-), 2.7 (1H, m, -CH-Ar), 2.5-1.5 (16H, m); *m/z* (E.I.) 300 (M^+, 5%), 158 (60).

(2R,3R)-1,7,7-Trimethyl-2-(1-Naphthyl)bicyclo[2,2,1]-hept-3-yl 2-oxocyclohexanecarboxylate **(79)**

The title compound was prepared from 4,7,7-trimethyl-3-(1-naphthalenyl)-bicyclo[2,2,1]hept an-2-ol **(49)**[56]. Chromatography on silica gel yielded the *ester* **(79)** (0.34g, 65%) as a colourless oil.(Found: M^+, 404.232. $C_{27}H_{32}O_3$ requires M, 404.235)υ_{max} (film)/cm^{-1} 3400, 1700, 1620; δ_H (270 MHz, $CDCl_3$) 11.85 (0.4H, s, enol OH), 8.20-7.40 (7H, m, ArCH), 5.50 (1H, d, *J*, 8.8 Hz, - CHOR), 4.20 (0.6H, m, -COCHCO-), 4.10 (1H, d, *J*, 8.8 Hz, -CH-Np), 2.00-1.20 (13H, m), 1.27 (3H, s, $-CH_3$), 1.25 (3H, s, $-CH_3$), 1.0 (3H, s, $-CH_3$); δ_C (68 MHz, $CDCl_3$) 135 (q), 129 (q), 128.7 (t), 127.4 (t), 127.0 (t), 126.5 (t), 125.0 (t), 124.3 (t), 123.4 (t), 79.6 (t), 42.5 (s), 29.1 (s), 26.4 (s), 24.0 (s), 23.8 (p), 22.0 (s), 21.7 (p), 21.6 (s), 14.8 (p); *m/z* (E.I.) 404 (M^+, 60%) 262 (80), 170 (100);

trans-2'-Phenylcyclohexyl 1-methyl-2-oxocyclohexanecarboxylate **(80)**

The title compound was prepared from β-keto ester **(78)** and iodomethane in toluene using procedure A in 35% yield, m.p. 62-65°C (from hexane) (Found: C, 76.7; H, 8.41; $C_{20}H_{26}O_3$ requires C, 76.4; H, 8.30%); υ_{max} ($CHCl_3$)/cm^{-1} 2920, 1700, 1420; δ_H (270 MHz, $CDCl_3$) 1:1 mixture of diastereomers, 7.4-7.1 (5H, m, ArCH), 5.10 (1H, m, -CHOR), 2.60 (1H, m, PhCH-), 2.40-1.20 (16H, m), 1.10 (1.5H, s, $-CH_3$), 0.80 (1.5H, s, $-CH_3$); *m/z* (C.I.) 315 (MH^+, 40%), 158 (100).

The title compound was also prepared from β-keto ester **(78)** using procedure B in 79% yield, procedure D (heated at 40°C) in 51%yield, and from enamine **(163)** in 100% nmr yield and 40% isolated yield *via* procedure E as a 1:1 mixture of diastereomers in all cases.

The product was shown to be identical by t.l.c. and spectroscopic methods to an authentic sample.

trans-2′-Phenylcyclohexyl 1-2″-propenyl-2-oxocyclohexanecarboxylate (**81**)

The title compound was prepared from β-keto ester (**78**) and 3-bromopropene in THF *via* procedure A in 84% yield, m.p. 84-87°C (from hexane) (Found: C, 77.8; H, 8.37. $C_{22}H_{28}O_3$ requires C, 77.6; H, 8.29%); υ_{max} ($CHCl_3$)/cm^{-1} 1700, 1430, 1250; δ_H (270 MHz, $CDCl_3$) (mixture of diastereomers) 7.3-7.1 (5H, m, ArCH), 5.6 (1H, m, CH_2=C<u>H</u>-), 5.15 (2H, m, CH_2=), 4.75 (1H, m, -CHOR), 2.7 (1H, m), 2.45 (1H, m), 2.3-1.0 (17H, m);δ_C (68 MHz, $CDCl_3$), 207 (q), 170.4 (q), 143.2 (q), 133.2, 133.0 (t), 128.4 (t), 127.5 (t), 126.5 (t, 118.0, 117.7 (s), 77.0 (t), 49.5 (t), 40.8, 40.3 (s), 39.4, 38.8 (s), 35.5 (s), 34.5, 33.9 (s), 32.1 (s), 27.4 (s), 25.6 (s), 24.5 (s), 21.9 (s); *m/z* (C.I.) 341 (MH^+, 15%), 183 (100).

The title compound was also prepared from β-keto ester (**78**) using procedure B in 44% yield, procedure C in 41% yield, and procedure D in 67% yield. The products were shown to be identical by t.l.c. and spectroscopic methods to an authentic sample.

trans-2′-Phenylcyclohexyl 1-(3″-bromo-2″-methylprop-2″-enyl)-2-oxocyclohexanecarboxylate (**85**)

The title compound was prepared from β-keto ester (**78**) and 1,3-dibromo-2-methylpropene in DME *via* procedure A in 42% yield as a colourless oil, b.p. (bulb to bulb) 220°C (0.1 mmHg). (Found: C, 64.0; H, 6.59. $C_{23}H_{29}BrO_3$ requires C, 63.7; H, 6.74%); υ_{max} (film)/cm^{-1} 2920, 1700, 1440; δ_H (270 MHz, $CDCl_3$) (mixture of 4 diastereomers, major and minor E and Z isomers as indicated) 7.40-7.10 (5H, m, ArCH), 5.95 (0.1H, d, *J* 1.5Hz, *E* minor

diastereomer), 5.85 (0.5H, m, *E*, major diastereomer), 5.42 (0.06H, m, *Z* minor diastereomer), 5.37 (0.33H, d, *J* 1.5 Hz, *Z* major diastereomer =CHBr), 5.10 (0.4H, dt, *J* 10, 6 Hz), 4.95 (0.6H, d t, *J* 10, 6 Hz -CHOR), 2.70-1.20 (19H, m), 1.70 (1H, d, *J* 1.5 Hz, *Z* major diastereomer), 1.63 (0.2H, d, *J* 1.5 Hz, *Z* minor diastereomer), 1.37 (1.5H, d, *J* 1.5 Hz, *E* major diastereomer), 1.15 (0.3H, d, *J* 1.5 Hz, *E* minor diastereomer =C-CH_3); *m/z* (C.I.) 435, 433 (MH^+, 5%), 354 (MH^+-Br, 10%), 159 (100).

The title compound was prepared using procedure C with 1,3-dibromo-2-methylpropene in 26% yield and shown to be identical by t.l.c. and spectroscopic methods to an authentic sample.

A solution of β-keto ester (**78**) (0.16 g, 0.53 mmol) in THF (1 ml) was added to a solution of LDA (0.6 mmol) in THF(1 ml) at -78°C and stirred for 0.5h. *n*-Butyllithium (0.38 ml, 1.6M in hexane, 0.6 mmol) was added dropwise and the mixture stirred for a further 0.5h. 1,3-Dibromo-2-methylpropene (0.3 g, 1.3 mmol) was added and the solution stirred for 1h at -78°C and then allowed to warm to room temperature for 6h. Work up as procedure B yielded the β-*keto ester* (**85**) (0.03 g, 12%) which was identical to a sample by t.l.c. and spectroscopic methods.

A solution of β-keto ester (**78**) (0.3 g, 1 mmol) in THF (1 ml) was added to a suspension of potassium hydride (0.13 g, 1.2 mmol) in THF (1.5 ml) at room temperature and stirred for 0.5h. The solution was cooled to -78°C and 1,3-dibromo-2-methylpropene (0.6 g, 3 mmol) was added and the mixture stirred for 1h and allowed to warm to room temperature for 6h. Work up as procedure A yielded the β-*keto ester* (**85**) (0.14 g, 33%) which was identical to a sample by t.l.c. and spectroscopic methods.

The title compound was prepared following the procedure of Kuwajima and Nakamura[70]. Benzyltrimethylammonium fluoride hydrate (1.5 equiv) was dried under vacuum with heating at 100°C for 8h. Nitrogen gas was introduced and the flask cooled. 4 Å molecular sieves (1 g) and dry THF (4 ml) were added and the mixture stirred overnight under a nitrogen atmosphere. A solution of silyl enol ether (**86**) (0.74 g, 2 mmol) and 1,3-dibromo-2-methylpropene (0.6 g, 3 mmol) in THF (2 ml) was added to the suspension and stirred for 3h. Filtration and removal of solvent under reduced pressure yielded an oil which was purified by flash column chromatography using ethyl acetate/petrol as eluent to yield the β-*keto ester* (**85**) (0.4 g, 40%) which was shown to be identical to a sample by t.l.c. and spectroscopic methods.

trans-2'-Phenylcyclohexyl 2-trimethylsilyloxy-1-cyclohexenecarboxylate (**86**)

Silyl enol ether (**86**) was prepared following the procedure of Torkelson and Ainsworth[69]. Hexamethyldisilazane (8 ml, 38 mmol), β-keto ester (**78**) (3 g, 10 mmol) and a catalytic amount of imidazole (0.13 g) were heated to reflux for 2h. Excess hexamethyldisilazane was removed by distillation to give a residue which was purified by bulb to bulb distillation yielding the silyl enol ether (**86**) (2.72 g, 74%) as a colourless oil , b.p. (bulb to bulb) 200°C (0.07 mmHg) (Found: C,70.6; H, 8.56; $C_{22}H_{32}O_3Si$ requires C, 70.9; H, 8.66%) υ_{max} (film)/cm^{-1} 2900, 1690, 1610, 1180; δ_H (270 MHz, $CDCl_3$) 7.2-7.0 (5H, m, ArCH), 4.95 (1H, *J* 10.5, 4.5 Hz, -CHOR), 2.8 (1H, m, -CHPh), 2.4-1.3 (16H, m), -0.3 (9H, s, $-Si(CH_3)_3$); *m/z* (C.I.) 301 (25%, MH^+-$SiMe_3$).

General procedure for phenylthioalkylation

Phenylthioalkylation was carried out following the procedure of Paterson and Fleming[71]. A catalytic amount (25 mg) of powdered anhydrous zinc bromide

was added to a solution of chlorosulphide (1 mmol) and silyl enol ether (1 mmol) in dry CH_2Cl_2 (2 ml) at room temperature and stirred for 5h. Concentration under reduced pressure followed by flash column chromatography on silica gel using ethyl acetate/petrol as eluent yielded the product.

Ethyl 1-benzenethiomethyl-2-oxocyclohexanecarboxylate **(90)**

The title compound was prepared from 1-carbethoxy-2-trimethylsilyloxy-1-cyclohexene **(89)**[73] and chloromethylphenylsulphide in 51% yield(0.15g). Further purification by bulb to bulb distillation yielded a colourless oil. b.p. (bulb to bulb) 150°C (0.2 mmHg) (Found : C, 66.0; H, 6.95; $C_{16}H_{20}O_3S$ requires C, 65.7; H, 6.90%); υ_{max} (film)/cm^{-1} 2920, 1700, 1250, 720; δ_H (270 MHz, $CDCl_3$) 7.5-7.05 (5H, m, ArCH), 4.0 (2H, m, $-CO_2C\underline{H}_2CH_3$), 3.5 (1H, d, *J* 18 Hz), 3.25 (1H, d, *J* 18 Hz $-CH_2SPh$), 2.65 (1H, m), 2.45 (2H, m), 2.05 (1H, m), 1.8-1.6 (4H, m) 1.05 (3H, t, $-CO_2CH_2C\underline{H}_3$); *m/z* (E.I.) 292 ($M^+$, 100%).

Ethyl 1-(3'-benzenethio-2'-methylprop-2'-enyl)-2-oxocyclohexanecarboxylate **(98)**

The title compound was prepared from 1-carbethoxy-2-trimethylsilyloxy-1-cyclohexene **(89)** and 1-benzenethio-3-chloro-2-methylpropene[75] in 27% yield(0.09g). υ_{max} (film)/cm^{-1} 2900, 1700, 1250, 720; δ_H (270 MHz, $CDCl_3$) 7.4-7.0 (5H, m, ArCH), 6.1 (0.6H, s, -C=CH-), 6.0 (0.4H, s, -C=CH-), 4.2 (2H, m, $-CO_2C\underline{H}_2CH_3$), 2.9 (1H, m), 2.6-1.9 (9H, m), 1.8 (3H, s, C=C-CH_3), 1.3 (3H, m, $-CO_2CH_2C\underline{H}_3$); δ_C (68 MHz, $CDCl_3$), 171.3 (q), 135.5 (q), 132.6 (q), 28.4 (t), 125.9 (t), 125.8 (t), 121.5, 121.2 (t), 61.4 (s), 60.0 (q), 41.1 (s), 37.8 (p),

36.3 (s), 27.6 (s), 22.5 (s), 20.7 (s), 19.5 (p); *m/z* (E.I.) 332 (M^+, 100%). **(98)** was not characterized by microanalysis or high resolution mass spectrometry.

trans 2'-Phenylcyclohexyl 1-benzenethiomethyl-2-oxocyclohexanecarboxylate **(101)**

The title compound was prepared from silyl enol ether **(86)** and chloro-methylphenylsulphide in 71% yield(0.3g). Further purification by bulb to bulb distillation yielded a colourless oil b.p. (bulb to bulb) 220°C (0.07 mmHg) (Found : C, 73.9; H, 7.46; $C_{26}H_{30}O_3S$ requires C, 73.9; H, 7.16%); υ_{max} (film)/cm^{-1} 2900, 1700, 720; δ_H (270 MHz, $CDCl_3$)(3:2 mixture of diastereomers) 7.4-7.0 (10H, m, ArCH), 5.1 (1H, m, -O-CH-), 3.22 (0.6H, d, *J* 12.8 Hz), 3.10 (0.6H, d, *J* 12.8 Hz), 2.98 (0.4H, d, *J* 12.8 Hz), 2.83 (0.4H, d, *J* 12.8 Hz, $-CH_2$-SPh), 2.7-1.2 (17H, m); *m/z* (C.I.) 422 (MH^+, 10%), 216 (80).

Ethyl 1-methyl-2-oxocyclohexanecarboxylate **(142)**[201]

An authentic sample was prepared following the method of Yanagita[201], from ethyl 2-oxocyclohexanecarboxylate and iodomethane with sodium ethoxide as the base (Procedure G) in 76% yield. υ_{max} (film)/cm^{-1} 2900, 1700, 1430; δ_H (270 MHz, $CDCl_3$) 4.19 (2H, dq, *J* 15, 6 Hz, $-CO_2C\underline{H}_2CH_3$), 2.3 (3H, m), 2.0 (1H, m), 1.7 (3H, m), 1.5 (1H, m), 1.29 (3H, s, $-CH_3$), 1.26 (3H, t, *J* 6 Hz - $CO_2CH_2C\underline{H}_3$); *m/z* (E.I.) 184 (M^+, 100%), 156 (100).

The title compound was also prepared from enamine **(139)** in 100% nmr yield, 79% isolated yield; enamine **(148)** in 80%, nmr yield and enamine **(149)** in 60% nmr yield *via* procedure E with iodomethane as the electrophile, and was identical to the authentic sample by t.l.c., g.c. and spectroscopic methods.

The title compound was prepared from the chiral enamine **(213)** and iodomethane using procedure F in 40% nmr yield and 32% isolated yield and was identical to an authentic sample by t.l.c., g.c. and spectroscopic methods. $[\alpha]^{21}_D$ - 7.8° (c, 1.28, EtOH). Enantiomeric excess was determined by n.m.r. using $Eu(hfc)_3$ as chiral shift reagent to be 33%. The methyl singlet (δ 1.26) was resolved into signals of ratio 2:1 (δ 1.63 (1H), 1.60 (2H)).

The β-keto ester **(142)** was prepared from the chiral enamine **(215)** and iodomethane using procedure H with THF as a cosolvent in 50% yield and was identical to an authentic sample by t.l.c, g.c. and spectroscopic methods. $[\alpha]^{23}_D$ + 70° (c, 6, EtOH). Enantiomeric excess was determined to be 55% by n.m.r. using Eu $(hfc)_3$ as chiral shift reagent . The methyl singlet (δ 1.26) was resolved into two signals of ratio 3.3:1 (δ 1.82 (2.3H), 1.78 (0.7H)).

Ethyl 3-methyl-2-oxocyclohexanecarboxylate **(144)**[82]

The title compound was prepared according to the method of Huckin and Weiler[82]. Ethyl 2-cyclohexananonecarboxylate (0.8 ml, 5 mmol) was added to a solution of LDA (11 mmol) in THF (15 ml) at 0°C and the solution stirred for 0.5h. Iodomethane (0.35 ml, 5 mmol) was added and the reaction stirred for 1h. After quenching with 2M HCl (15 ml), the mixture was extracted with ethyl acetate (3 x 15 ml). The combined organic phases were washed with saturated aq. $NaHCO_3$ (15 ml), brine (15 ml) and dried (Na_2SO_4). Removal of solvent under reduced pressure yielded an oil which was purified by distillation to yield the β-*keto ester* **(144)** (0.76 g, 83%) as a colourless oil, b.p. 118°C (15 mmHg) [Lit.[202] b.p. 115°C (12 mmHg)]. υ_{max} (film)/cm^{-1} 3000, 1700, 1600; δ_H (270 MHz, $CDCl_3$) (3:1 mixture keto:enol) 12.38 (0.25H, s, enol OH), 4.20 (2H, m, $-CO_2C\underline{H}_2CH_3$), 3.40 (0.75H, m, $-CO-C\underline{H}-CO_2R$), 2.50-1.50 (7H, m), 1.3 (3H, m, $-CO_2CH_2CH_3$), 1.04 (3H, d, *J*

6.5 Hz, -CH-CH_3); *m/z* (E.I.) 184 (M^+, 100%).

Ethyl 1-2'-propenyl-2-oxocyclohexanecarboxylate (**4**)[3]

The title compound was prepared from ethyl 2-oxocyclohexanecarboxylate and 3-bromopropene using sodium ethoxide as base (Procedure G) in 74% yield. υ_{max} (film)/cm^{-1} 2920, 1700, 1630; δ_H (270 MHz, $CDCl_3$) 5.75 (1H, m, =CH), 5.08 (1H, m, $=CH_2$), 5.00 (1H, m, $=CH_2$), 4.20 (2H, q, *J* 7 Hz, $-CO_2C\underline{H}_2CH_3$), 2.60 (1H, dd, *J* 14, 7 Hz $-CH_2$-CO-), 2.45 (3H, m), 2.32 (1H, dd, *J* 14, 7 Hz, $-CH_2$-CO-), 2.0 (1H, m), 1.70 (3H, m), 1.45 (1H, m), 1.25 (3H, t, *J* 7 Hz, $-CO_2CH_2CH_3$); *m/z* (C.I.) 211 (MH^+, 100%).

The title compound was prepared from enamine **(139)** in 85% nmr yield and 62% isolated yield, enamine **(148)** in 30% nmr yield, and enamine **(149)** in 50% nmr yield *via* procedure E using 3-bromopropene as electrophile. Also, from enamine **(148)** in 70% nmr yield and enamine **(149)** in 85% nmr yield *via* procedure F with 3-bromopropene as electrophile, and was shown to be identical to an authentic sample by t.l.c, g.c. and spectroscopic methods.

The title compound was prepared from chiral enamine **(213)** and 3-bromopropene using procedure F in 100% nmr yield and 46% isolated yield. It was identical to an authentic sample by t.l.c, g.c. and spectroscopic methods. $[\alpha]^{25}_D$ + 12° (*c*, 2, $CHCl_3$). [Lit[161]: $[\alpha]^{22}_D$ - 100.4° (*c*, 0.87, $CHCl_3$), enantiomeric excess, 76%, by chiral shift nmr]. Enantiomeric excess was estimated to be 15% by nmr using $Eu(hfc)_3$ as chiral shift reagent The multiplets at δ 5.08, 5.00 were resolved into two groups of signals of ratio 1.3:1 (δ 5.18 (0.6H, m), 5.1 (0.9H, m), 5.08 (0.6H, m)).

The title compound was prepared from chiral enamine **(215)** and 3-bromopropene via procedure H using dioxolane as cosolvent in 32% yield and was identical to an authentic sample by t.l.c, g.c. and spectroscopic methods. $[\alpha]^{20}_{D}$ + 4.15° (*c*, 2, $CHCl_3$).

Ethyl 1-3'-bromo-2'-methylprop-2'-enyl-2-oxocyclohexanecarboxylate **(143)**

The title compound was prepared from ethyl 2-oxocyclohexanecarboxylate and 1,3-dibromo-2-methylpropene using sodium ethoxide as base (Procedure G) in 70% yield. υ_{max} (film)/cm^{-1} 2920, 1720, 1640; δ_H (270 MHz, $CDCl_3$). (2:1 mixture of isomers) 5.95 (1H, m =CHBr), 4.15 (2H, m, $-CO_2C\underline{H}_2CH_3$), 2.60-2.20 (6H,m), 1.78 (2H, d, *J* 1Hz, $=C-CH_3$), 1.77 (1H, d, *J* 1 Hz, $=C-CH_3$), 1.7-1.54 (4H, m), 1.1 (3H, m, $-CO_2CH_2C\underline{H}_3$); δ_C (68 MHz, $CDCl_3$) 174.8 (q), 173 (q), 138.7 (q), 103, 102.5 (t), 60.1 (s), 54.0 (q), 40.9 (s), 33.8 (s), 31.4 (s), 26.5 (s), 22.0 (s), 22.0, 18.6 (p), 14.0 (p); *m/z* (C.I.) 305, 303 (MH^+, 5%), 171 (100).

The title compound was prepared from enamine **(139)** and 1,3-dibromo-2-methylpropene via procedure E in 26% nmr yield and 20% isolated yield and procedure F in 40% nmr yield and was shown to be identical to the authentic sample by t.l.c, g.c. or spectroscopic methods.

The title compound was prepared from chiral enamine **(213)** and 1,3-dibromo-2-methylpropene in 67% nmr yield, 27% isolated yield *via* procedure F, and was shown to be identical to the authentic sample by t.l.c, g.c. and spectroscopic methods. $[\alpha]^{20}_{D}$ + 2.5° (*c*, 9, $CHCl_3$). Enantiomeric excess was determined to be 15% by nmr using $Eu(hfc)_3$ as chiral shift reagent. The methyl doublet of the (Z)-isomer (δ 1.78) was resolved into two signals of ratio 1:1.3 (δ 1.84 (1.7H, d), 1.78 (1.3H, d)).

The β-keto ester (**143**) was prepared from chiral enamine (**215**) and 1,3-dibromo-2-methylpropene in 54% yield *via* procedure H with dioxolane as cosolvent. $[\alpha]^{20}_{D}$ - 2.1°, (*c*, 5, $CHCl_3$).

Ethyl 1-propyl-2-oxo-cyclohexanecarboxylate (**145**)[105]

The title compound was prepared from enamine (**139**) and iodopropane in 40% nmr yield *via* procedure E. υ_{max} (film)/cm^{-1} 2920, 1700, 1630; δ_H (270 MHz, $CDCl_3$) 4.20 (2H, q, *J* 7 Hz, $-CO_2C\underline{H}_2CH_3$), 2.5-1.5 (12H, m), 1.3 (3H, t, *J* 7 Hz, $-CO_2CH_2C\underline{H}_3$), 0.92 (3H, t, *J* 7 Hz, $-CH_2C\underline{H}_3$); *m/z* (E.I.) 212 (M^+, 5%), 170 (100).

Ethyl 1-phenylmethyl-2-oxocyclohexanecarboxylate (**146**)[3]

The title compound was prepared from enamine (**139**) and benzyl bromide in 55% nmr yield, 42% isolated yield using procedure E. υ_{max} (film)/cm^{-1} 2920, 1700; δ_H (270 MHz, $CDCl_3$) 7.4-7.0 (5H, m, ArCH), 4.08 (2H, m, $-CO_2C\underline{H}_2CH_3$), 3.31 (1H, d, *J* 14 Hz, $-CH_2Ph$), 2.86 (1H, d, *J* 14 Hz, $-CH_2Ph$), 2.46 (3H, m), 2.00 (1H, m), 1.65 (3H, m), 1.45 (1H, m), 1.16 (3H, t, *J* 7 Hz, $-CO_2CH_2C\underline{H}_3$); *m/z* (E.I.) 260 ($M^+$, 10%), 181 (100).

1',1'-Ethyloxymethyloxycarbonyloxy-1-methylenyl-2-piperidinyl-cyclohex-2-ene (**147**)

To a solution of LDA (3 mmol) in THF (2 ml) at -78°C was added the enamine (**139**) (0.47 g, 2 mmol) in THF (1 ml). After 0.5h, methylchloroformate (0.3 ml, 4 mmol) was added and after 0.5h, the reaction was allowed to warm to room temperature over 6h. The solvent was removed

under reduced pressure and the residue taken up in hexane and filtered. Removal of solvent under reduced pressure yielded an oil which was shown to be a 1:1 mixture of *carbonate* **(147)** and starting enamine **(139)** by n.m.r. which was not purified. δ_H (270 MHz, $CDCl_3$) (carbonate signals from mixture)5.12 (1H, t, *J* 4 Hz, -HC=C-N-), 4.25 (2H, m, $-CO_2C\underline{H}_2CH_3$), 3.65 (3H, s, $-CO_2CH_3$), 3.0-1.5 (16H, m), 1.30 (3H, m, $-CO_2CH_2CH_3$); *m/z* (E.I.) 295 (M^+, 100%), 211 (80).

Ethyl 1-Methyl-2-oxocyclopentanecarboxylate **(154)**[203]

Ethyl 2-oxocyclopentanecarboxylate (0.44 ml, 3 mmol) in THF (6 ml) was added to a suspension of sodium hydride (60%) (0.14 g, 3.5 mmol) in THF (5 ml) at 0°C and stirred for 0.5h. Iodomethane (0.25 ml, 3.5 mmol) was added and the mixture stirred for 2h. After quenching with water (10 ml), the mixture was diluted with ethyl acetate (10 ml) and the layers separated. The aqueous phase was washed with ethyl acetate (10 ml) and the combined organic phases were washed with saturated brine (10 ml). After drying ($MgSO_4$), removal of solvent under reduced pressure gave an oil which was purified by flash column chromaography on silica gel with ethyl acetate/petrol as eluent to yield the β-*keto ester* **(154)**[203] as a colourless oil (0.34 g, 85%). υ_{max} (film)/cm^{-1} 2960, 1730, 1440; δ_H (270 MHz, $CDCl_3$) 4.15 (2H, dq, *J* 7, 1 Hz, $-CO_2C\underline{H}_2CH_3$), 2.40 (2H, m), 1.95 (4H, m), 1.31 (3H, s, $-CH_3$), 1.25 (3H, t, *J* 7 Hz, $-CO_2CH_2C\underline{H}_3$); *m/z* (C.I.) 171 ($MH^+$, 95%), 142 (75), 125 (100).

The title compound was prepared from enamine **(151)** in 90% nmr yield and enamine **(152)** in 43% nmr yield using procedure F with iodomethane as electrophile and was shown to be identical to the authentic sample by t.l.c, g.c. or spectroscopic methods.

Ethyl 1-2'-propenyl-2-oxocyclopentanecarboxylate **(155)**[107]

The title compound was prepared from enamine **(150)** and 3-bromopropene *via* procedure F in 100% nmr yield. υ_{max} (film)/cm^{-1} 2960, 1740, 1640, 1440; δ_H (270 MHz, $CDCl_3$) 5.7 (1H, m, =CH), 5.1 (2H, m, $=CH_2$), 4.15 (2H, q, *J* 7 Hz, $-CO_2C\underline{H}_2CH_3$), 2.65 (1H, m), 2.5-2.2 (4H, m), 2.1-1.9 (3H, m), 1.25 (3H, t, *J* 7 Hz, $CO_2CH_2C\underline{H}_3$); *m/z* (C.I.) 197 (MH^+, 100%), 168 (30).

β-Keto ester **(155)** was also prepared from enamine **(151)** in 40% nmr yield and enamine **(152)** in 100% nmr yield using procedure F and 3-bromopropene as electrophile and the product was identical by t.l.c, g.c. and spectroscopic methods to an authentic sample.

Ethyl 1-(3'-bromo-2'-methylprop-2'-enyl)-2-oxycyclopentanecarboxylate **(156)**

The title compound was prepared from enamine **(150)** and 1,3-dibromo-2-methylpropene using procedure F in 50% nmr yield, 16% isolated yield. (Found: M^+-Br, 209.120; $C_{12}H_{17}O_3$ requires M^+-Br,209.118); υ_{max} (film)/cm^{-1} 2960, 1720, 1625; δ_H (270 MHz, $CDCl_3$) (2:1 mixture of isomers - E and Z) 6.0 (1H, s, =CHBr), 4.1 (2H, q, *J* 7 Hz, $-CO_2C\underline{H}_2CH_3$), 2.6-1.8 (8H, m), 1.78 (1H,d, *J* 1.2 Hz, $=C-CH_3$), 1.73 (2H, d, *J* 1.2 Hz, $=C-CH_3$), 1.2 (3H, t, *J* 7 Hz, $-OCH_2CH_3$); δ_C (68 MHz, $CDCl_3$) 215 (q), 170 (q), 137 (q), 105 (t), 61 (q), 41 (s), 37 (p), 32 (s), 20 (s), 19 (s), 17 (s), 14 (p); *m/z* (C.I.) 291 (MH^+, 55%), 289 (MH^+, 60); (E.I.) 209 (M^+-Br, 100).

Methyl 1-methyl-2-oxocycloheptanecarboxylate **(157)**

Methyl 2-oxocycloheptanecarboxylate[104] (0.5 g, 3 mmol) in THF (4 ml) was added to a suspension of sodium hydride (0.13 g, 3.3 mmol, 60% in mineral

oil) in THF (2 ml) at 0°C and stirred for 0.5h. Iodomethane (0.2 ml, 3 mmol) was added and the reaction stirred for 4h. After quenching by addition of water (5 ml) the mixture was diluted with ethyl acetate (5 ml) and the phases separated. The aqueous phase was extracted with ethyl acetate (2 x 5 ml) and the combined organic phases were washed with brine (5 ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded an oil which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the β-*keto ester* (**157**) (0.3 g, 54%) as an oil. υ_{max} (film)/cm^{-1} 2920, 1700, 1430; δ_H (270 MHz, $CDCl_3$) 3.71 (3H, s, $-CO_2CH_3$), 2.85 (1H, m, $-CH_2CO-$), 2.50 (1H, m, $-CH_2CO-$), 2.15 (1H, m), 1.85-1.5 (7H, m), 1.35 (3H, s, $-CH_3$); *m/z* (C.I.) 185 (MH^+, 100%), 153 (50).

The title compound was also prepared from enamine (**153**) and iodomethane *via* procedure F in 70% nmr yield and was shown to be identical to an authentic sample by t.l.c, g.c. and spectroscopic methods.

Methyl 1-2'-propenyl-2-oxocycloheptanecarboxylate (**158**)[204]

The title compound was prepared from enamine (**153**) and 3-bromopropene using procedure F in 67% nmr yield and 30% isolated yield. υ_{max} (film)/cm^{-1} 2900, 1730, 1640, 1440; δ_H (270 MHz, $CDCl_3$) 5.7 (1H, m, = CH), 5.08 (1H, m, = CH), 5.05 (1H, m, = CH), 3.71 (3H, s, - $CO_2CH_2CH_3$), 2.8-2.0 (6H, m), 1.9-1.6 (6H, m); *m/z* (E.I.) 210 (M^+, 70%), 170 (100).

trans 2'-Phenylcyclohexyl 2-piperidine-1 or 2-cyclohexenecarboxylate (**163**)

β-Keto ester (**78**) (3.5 g, 11 mmol), piperidine (5.5 ml, 55 mmol), and a catalytic amount of p-toluenesulphonic acid (0.1 g), were heated in benzene at reflux for 7 days with water separation. Benzene and excess piperidine were

removed under reduced pressure. The residue was purified by bulb to bulb distillation yielding the *enamine* **(163)** (1.47 g, 36%) as a yellow oil; b.p. (bulb to bulb) 250°C (0.1 mmHg); υ_{max} (film)/cm^{-1} 2920, 1700, 1660; δ_H (270 MHz, $CDCl_3$) (75:25 mixture of isomers) 7.2-7.0 (5H, m, ArCH), 5.0 (1H, m, -C<u>H</u>-OR), 4.75 (0.25H, t, *J* 4 Hz CH=C-N), 3.8-1.2 (27H, m, - aliphatic CH_2); δ_C (68 MHz, $CDCl_3$) 143 (q), 128.5 (t), 127.9 (t), 126.3 (t), 103.6 (t), 75 (t), 51 (t), 46 (t), 51 (s), 49 (s), 47 (s), 35-15 (s, aliphatic CH_2); *m/z* (C.I.) 367 (MH^+, 5%), 210 (50), 159 (100). **(163)** was not characterized by microanalysis or high resolution mass spectrometry.

Methyl 2-methyl-3-oxopentanoate **(166)**[106]

To a solution of LDA (5.5 mmol) in THF (10 ml) at -78°C was added methyl 3-oxopentanoate (0.65 ml, 5 mmmol) in THF (5 ml) and stirred for 0.5h. Iodomethane (0.9 ml, 15 mmol) was added and after a further 0.5h, the mixture was allowed to warm to room temperature. After 3h, the reaction was quenched with water (5 ml), and extracted with ethyl acetate, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield an oil (0.78g) which was a 1:1 mixture of methyl 3-oxopentanoate and β-*keto ester* **(166)** which was not purified. δ_H (270 MHz, $CDCl_3$) (**(166)** signals from mixture) 3.80 (3H, s, $-COCH_3$, 3.60 (1H, q, *J* 7Hz, -C<u>H</u>-CH_3), 2.50 (2H, q, *J* 7Hz, $-CH_2$-CO-), 1.1 (6H, m, -C<u>H</u>-CH_3, $-CH_2$-C<u>H</u>$_3$)

Methyl 2-methyl-3-oxopentanoate **(166)**[106] *and Methyl 4-methyl-3-oxopentanoate* **(167)**[107]

The title compounds were prepared from methyl 3-pyrrolidinyl-2-pentanoate **(128)** (0.9 g, 5 mmol) and iodomethane (0.6 ml, 10 mmol) *via* Procedure E, as an oil (0.7 g) which was a 2:1 mixture of β-*keto ester* **(166)** and β-*keto ester*

(167) which was not purified.

(167) δ_H (270 MHz, $CDCl_3$) (from mixture) 3.80 3H, s, $-COCH_3$), 3.5 (2H, s, $-CO-CH_2-$), 2.5 (1H, m, $-CH(CH_3)_2$), 1.15 (6H, d, *J* 7.5 Hz, $-CHCH_3$).

(166) was identical to the authentic sample by ^1H nmr.

(2R,5R)-2,5-Dimethylpyrrolidine Hydrochloride **(183))**

To a solution of (-)-N-benzyl-(2R,5R)-2,5-dimethylpyrrolidine **(182)**[120] (2 g, 11 mmol) in dry methanol (40 ml) was added 10% $Pd(OH)_2$ on carbon (0.5 g). The resulting mixture was stirred vigorously under an atmosphere of hydrogen for 2h[123]. The catalyst was removed by filtration through celite and washed with methanol (2 x 5 ml). The solution was acidified with ethanolic HCl and the solvent removed under reduced pressure to give a pale brown gum which was triturated with ether to give a pale pink solid. Recrystallisation from acetone-methanol-ether yielded the *pyrrolidine hydrochloride* **(183)** (0.6 g, 50%) as a colourless solid. m.p. 196-198°C (from acetone-methanol-ether); $[\alpha]^{19}_D$ + 5.0° (*c*, 3.0, CH_2Cl_2) [Lit[117]. m.p. 197-200°C, $[\alpha]^{24}_D$ + 5.47° (*c*, 3.0, CH_2Cl_2)]. δ_H (270 MHz, $CDCl_3$) 9.6-9.4 (2H, br s, -NH. HCl), 3.9-3.75 (2H, m, -NH-C<u>H</u>-CH_3), 2.30-2.10 (2H, m), 1.70-1.60 (2H, m), 1.52 (6H, d, *J* 6.6 Hz, -CHC<u>H</u>$_3$).

(-)-(2R,5R)-2,5-dimethylpyrrolidine **(178)** was generated from the hydrochloride **(183)** as an ethereal solution. To a stirred suspension of hydrochloride **(183)** (3 g, 22 mmol) in dry ether (25 ml) was added *n*-butyllithium (13.8 ml, 22 mmol, 1.6M in hexane). After 1h, the reaction mixture was filtered to yield the pyrrolidine **(178)** as the filtrate which was used as an ethereal solution.

dl-Diethyl α,δ-dibromoadipate **(187)**

The title compound was prepared using the method of Guha and Sankaran[133]. The diester was a mixture of meso and *dl-isomer*. Meso isomer crystallized on standing and was removed by filtration to give the dl-isomer as an oil (50%). δ_H (270 MHz, $CDCl_3$) 4.26 (6H, m, $-CO_2C\underline{H}_2CH_3$, -CHBr-), 2.16 (4H, m, $-CH_2-$), 1.32 (6H, t, J 7 Hz, $-CO_2CH_2C\underline{H}_3$).

Meso diethyl α,δ-dibromoadipate **(187)** (50%) m.p. 62-64°C (from ethanol) [Lit[135]. m.p. 64-66°C] δ_H (270 MHz, $CDCl_3$) 4.25 (6H, m, $-CO_2C\underline{H}_2CH_3$, -CHBr), 2.32 (2H, m), 2.06 (2H, m), 1.32 (6H, t, *J* 7 Hz, $-CO_2CH_2C\underline{H}_3$).

trans-Dimethyl-N-benzylpyrrolidine-2,5-dicarboxylate **(184)**

The title compound was prepared using the method of Cignarella and Nathansohn[132]. dl Ethyl-α,δ-dibromoadipate **(187)** (50 g, 138 mmol) in benzene (150 ml) was heated to reflux. The heating was immediately discontinued and benzylamine (50 ml, 458 mmol) was added with stirring over 15 mins. and left to stand overnight and then refluxed for 6h. The reaction mixture was cooled and benzylamine hydrobromide was removed by filtration. The filtrate was concentrated under reduced pressure to give a residue which was distilled under vacuum to give the *pyrrolidine* **(184)**[131] (20 g, 48%) as a colourless oil, b.p. 128-135°C (0.04 mmHg); δ_H (270 MHz, $CDCl_3$) 7.4-7.2 (5H, ArCH), 4.11 (4H, q, *J* 7 Hz, $-CO_2C\underline{H}_2CH_3$), 4.05-3.75 (4H, m, $-CH_2Ph$,-CHN-), 2.35-1.88 (4H, m, $-CH_2-$), 1.24 (6H, t, *J* 7 Hz, $-CO_2CH_2C\underline{H}_3$).

trans N-Benzyl-2,5-bispyrrolidinemethanol **(199)**

The pyrrolidine diester **(184)** (3.8 g, 12.5 mmol) in dry ether (10 ml) was added to a slurry of lithium aluminium hydride (1 g, 26 mmol) in dry ether (25 ml) at 0°C and stirred for 2h. 2M NaOH (5 ml) was added dropwise and the mixture filtered through celite. The filtrate was dried (Na_2SO_4) and removal of solvent under reduced pressure yielded the *diol* **(199)** (2.47 g, 89%) as an oil which was used without further purification. υ_{max} (film)/cm^{-1} 3400, 2920; δ_H (270 MHz, $CDCl_3$) 7.4-7.2 (5H, m, ArCH), 3.86 (2H, s, $PhCH_2$-), 3.55 (4H, m, -$C\underline{H}_2OH$), 3.16 (2H, m, -CHN-), 2.37 (2H, br s, -OH), 2.0-1.8 (4H, m, -CH_2-).

trans N-Benzyl-2,5-bis(methoxymethyl)pyrrolidine **(200)**

The diol **(199)** (2.8 g, 13 mmol) in THF (15 ml) was added to a suspension of sodium hydride (0.52 g, 13 mmol; 40% in mineral oil) in THF (15 ml) at 0°C and then stirred at room temperature for 2h. Iodomethane (0.8 ml, 13 mmol) was added and the reaction stirred 3.5h. The reaction was quenched by addition of saturated NH_4Cl (aq) (5 ml) and water (20 ml) and ethyl acetate (20 ml) were added and the phases separated. The aqueous phase was extracted with ethyl acetate (20 ml) and the combined organic phases were washed with brine (20 ml) and dried (Na_2SO_4). Removal of solvent under reduced pressure gave a residue which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the *pyrrolidine* **(200)** (0.63 g, 20%) as an oil. υ_{max} ($CHCl_3$)/cm^{-1} 2900, 2860, 1440; δ_H (270 MHz, $CDCl_3$) 7.4-7.2 (5H, m, ArCH), 3.90 (2H, s, -CH_2Ph), 3.4-3.0 (6H, m, -N$C\underline{H}$-$C\underline{H}_2O$), 3.26 (6H, s, -OCH_3), 1.85 (2H, m), 1.60 (2H, m); *m/z* (C.I.) 250 (MH^+, 15%), 204 (100).

Trans 2,5-bismethoxymethylpyrrolidine hydrochloride **(202)**[128]

To a solution of the pyrrolidine **(200)** (0.63 g, 2.5 mmol) in methanol (10 ml) was added 10% Pd $(OH)_2$ on carbon (0.2 g). The resulting mixture was stirred vigorously under an atmosphere of hydrogen for 12h. The catalyst was removed by filtration through celite and washed with methanol (2 x 2 ml). Ethanolic HCl was added until the solution became acid and the solvent was removed under reduced pressure to yield a purple gum. Trituration with ether yielded the *pyrrolidine hydrochloride* **(209)** (0.35 g, 72%) as a pale pink solid. δ_H (270 MHz, $CDCl_3$) 9.80 (2H, brs, -NH.HCl), 4.00 (2H, m, -C<u>H</u>N-), 3.8-3.6 (4H, m, $-OCH_2-$), 3.40 (6H, s, $-OCH_3$), 2.2-1.8 (4H, m, $-CH_2$).

Ethyl 2-(S)-2'-methoxymethylpyrrolidinyl-1-cyclohexenecarboxylate **(213)**

The enamine was prepared using the method of Weinreb.[143] To a mixture of ethyl 2-oxocyclohexanecarboxylate (0.6 ml, 4 mmol) and 1-trimethylsilyl-(S)-2-methoxymethylpyrrolidine **(214)** (1.5 g, 8 mmol) was added a catalytic amount ofp-toluenesulphonic acid (0.1 g) and the mixture stirred at room temperature under a nitrogen atmosphere for 40h. The resulting mixture was purified by bulb to bulb distillation to yield the *enamine* **(213)** (0.71 g, 67%) as a colourless oil. b·p. (bulb to bulb) 200°C (0.6 mmHg). υ_{max} (film)/cm^{-1} 2934, 1737, 1679, 1217; δ_H (270 MHz, $CDCl_3$) 4.6 (0.1H, m, -C=CH-), 4.2 (2H, m, $-CO_2C\underline{H}_2CH_3$), 3.4-3.2 (4H, m, -N-C<u>H</u>-, $-O-CH_2-$, $-N-CH_2-$), 3.3 (3H, s, $-OCH_3$), 2.95 (1H, m), 2.6-1.4 (12H, m, $-CH_2-$), 1.3 (3H, m, $-CO_2CH_2C\underline{H}_3$); δ_C (68 MHz, $CDCl_3$) 168.0 (q), 164.7 (q), 140.0 (q), 74.9 (s), 59.0 (t), 58.8 (p), 57.2 (s), 53.2 (s), 41.8 (s), 29.9 (s), 27.7 (s), 27.1 (s), 25.2 (s), 23.2 (s), 14.2 (p).

A solution of ethyl 2-oxocyclohexanecarboxylate (4 g, 26 mmol) and (S)-2-methoxymethylpyrrolidine (3 g, 26 mmol) were heated to reflux with a catalytic amount of p-toluenesulphonic acid under water separation for 3 days. Solvent was removed under reduced pressure and the residue was purified by bulb to bulb distillation to yield the *enamine* **(213)** (4.7 g, 68%) as a yellow oil (b.p. (bulb to bulb) 150°C/ 0.04 mmHg).

1-Trimethylsilyl-(S)-2-methoxymethylpyrrolidine **(214)**

(S)-2-Methoxymethylpyrrolidine **(212)**[159,160] (3.4 g, 30 mmol) and hexamethyldisilazane (3.2 ml, 15 mmol) and catalytic chlorotrimethylsilane (0.05 ml) were heated together in an oil bath at 150°C for 5h. The resulting mixture was distilled to yield the *silylpyrrolidine* **(214)** (2.4 g, 43%) as a colourless oil, b.p. 67-72°C (20 mmHg). δ_H (270 MHz, $CDCl_3$) 3.25 (3H, s, $-OCH_3$), 3.1 (3H, m, $-OCH_2$-, -N-CH-), 2.8 (2H, m, $-CH_2$-N-), 1.6 (3H, m, $-CH_2$-), 1.25 (1H, m, $-CH_2$), 0.1 (9H, s, $-Si(CH_3)$).

Ethyl (S)-2-[1-[(1,1-dimethylethoxy)carbonyl]-2-methyl-propyl]-amino]-1-cyclohexene-1-carboxylate **(215)**

A solution of ethyl 2-oxocyclohexanecarboxylate (3.5 ml, 22 mmol) and (S)-valine tert-butyl ester[162,163] (3 g, 17 mmol) in benzene (80 ml) was heated at reflux with p-toluenesulphonic acid (0.5 g) with water separation for 24h[6]. Benzene was removed under reduced pressure to yield a residue which crystallised on standing and purified by recrystallisation from ethyl acetate-hexane to yield the *enamine* **(215)** (5 g, 92%) as colourless cubes. m.p. 72-75°C (from ethyl acetate-petrol), $[\alpha]^{22}_D$ 53.9° (*c*, 2, $CHCl_3$). υ_{max} ($CHCl_3$)/cm^{-1} 3240, 2900, 1710, 1630, 1590; δ_H (270 MHz, $CDCl_3$) 9.2 (1H, d, *J* 9 Hz, -NH-) 4.13 (2H, q, *J* 7 Hz, $-CO_2\underline{CH_2}CH_3$), 3.78 (1H, dd, *J* 9, 6 Hz,

-NH-C<u>H</u>-), 2.30 (4H, m, -CH=CH-C<u>H</u>$_2$-), 1.60 (4H, m, -C<u>H</u>$_2$-), 1.45 (9H, s, -(C<u>H</u>$_3$)$_3$), 1.26 (3H, t, *J* 7 Hz, -CO$_2$CH$_2$C<u>H</u>$_3$), 1.01 (6H, dd, *J* 6, 2 Hz, -CH-(C<u>H</u>$_3$)$_2$); *m/z* (E.I.) 325 (M^+, 100%), 224 (70).

Methyl 1-(3'-bromo-2'-methylprop-2'-enyl)-2-oxo-1,2,3,4-tetrahydro-1-naphthalenecarboxylate **(239)**

The title compound was prepared from methyl 2-oxo-1,2,3,4-tetrahydro-1-naphthalenecarboxylate **(230)**[181] (2 g, 10 mmol) and 1,3-dibromo-2-methylpropene (0.22 g, 11 mmol) using procedure D in 74% yield, as an oil; b.p. (bulb to bulb) 250°C (0.2 mmHg) (Found: C, 57.4; H, 5.10; $C_{16}H_{17}BrO_3$ requires C, 57.0; H, 5.08%); υ_{max} (film)/cm^{-1} 2940, 1730, 1610, 1430; δ_H (270 MHz, $CDCl_3$) (3:2 mixture of isomers) 7.4-7.1 (4H, m, ArCH), 5.69 (0.4H, s) and 5.30 (0.6H, s, =CHBr), 3.64 (1.2H, s) and 3.63 (1.8H, s, -CO$_2$C<u>H</u>$_3$), 3.37 (1H, d, *J* 14 Hz), 3.2-2.4 (5H, m), 1.4 (1.2H, s) and 1.2 (1.8H, s, =C-C<u>H</u>$_3$); *m/z* (C.I.) 337, 339 (MH^+, 80%).

Methyl 1-(3'-bromo-2'-methylprop-2'-enyl)-2-trimethylsilyloxy-1,4- dihydro-1-naphthalenecarboxylate **(240)**

The β-ketoester **(239)** (1.43 g, 4.2 mmol) in THF was added to a solution of LDA (4.6 mmol) in THF (5 ml) at 0°C and stirred for 1h. Chlorotrimethylsilane (1.06 ml, 8.4 mmol) was added and the reaction stirred for a further 1h. The mixture was diluted with petrol (10 ml) and washed with ice cold water (5 ml). After drying, removal of solvent under reduced pressure yielded the *silyl enol ether* (1.5 g, 86%) as a pale yellow oil which was further purified by bulb to bulb distillation, b.p. 250°C (0.2 mmHg). υ_{max} (film)/cm^{-1} 2940, 1735, 1680, 1230, 840; δ_H (270 MHz, $CDCl_3$) (3:2 mixture of isomers) 7.2-6.9 (4H, m, ArCH), 5.56 (0.4H, s, =CHBr (*Z*)), 5.23 (0.6H, s, =CHBr (*E*)),

4.85 (0.6H, t, *J* 2 Hz, -CH=COSiMe$_3$), 4.82 (0.4H, t, *J* 2 Hz, -CH=COSiMe$_3$), 3.4 (3H, s, -CO_2CH_3), 3.2 (2H, d, *J* 2 Hz, benzylic CH_2), 2.87 (1H, d, *J* 15 Hz, -CH_2-C=CHBr), 2.55 (1H, d, *J* 15 Hz, -CH_2C=CHBr), 1.1 (3H, s, -CH_3), 0.0 (9H, s, -OSi(CH_3)$_3$); *m/z* (C.I.) 411, 409 (MH^+, 50%), 329 (MH^+-HBr, 100).

Methyl 1-(2'-methylprop-2'-enyl)-2-oxo-1,2,3,4-tetrahy dro-1-naphthalenecarboxylate **(242)**

The title compound was prepared from methyl 2-oxo-1,2,3,4-tetrahydro-1-naphthalenecarboxylate **(230)** (2 g, 10 mmol) and 3-chloro-2-methylprop-1-ene (1.5 ml, 15 mmol) using procedure D in 58% yield(1.5 g) as an oil b.p. (bulb to bulb) 200°C (0.1 mmHg) (Found: C, 74.1; H, 7.11; $C_{16}H_{18}O_3$ requires C, 74.4; H, 7.02%); υ_{max} (film)/cm^{-1} 2940, 1750, 1420; δ_H (270 MHz, $CDCl_3$) 7.4-7.2 (4H, m, ArCH), 4.67 (1H, s, =CH_2), 4.45 (1H, s, CH_2=C-), 3.6 (3H, s, -CO_2CH_3), 3.25 (1H, d, *J* 13.5 Hz, -$\underline{CH}_2$-C=CH_2), 3.08 (2H, t, *J* 6.8 Hz, -CH_2-), 2.86 (1H, m), 2.85 (1H, d, *J* 13.5 Hz, -CH_2-C=CH_2), 2.7 (1H, m, -CH_2-), 1.3 (3H, s, -CH_3); *m/z* (E.I.) 258 (M^+, 100%), 240 (70).

Methyl 1-(2'-methylprop-2'-enyl)-2-trimethylsilyloxy-1,4-dihydro-1-napthalenecarboxylate **(243)**

β-Keto ester **(242)** (1 g, 3.8 mmol) in THF (6 ml) was added to a suspension of potassium hydride (35%) (0.48 g, 4.2 mmol) in THF (4 ml) at 0°C. After 0.5h, chlorotrimethylsilane (1 ml, 7.6 mmol) was added and the mixture allowed to warm to room temperature and stirred for 4h. The reaction mixture was diluted with petrol (10 ml) and washed with ice cold water (5 ml), dried ($MgSO_4$) and solvent removed under reduced pressure to yield the *silyl enol ether* **(244)** (0.8 g, 64%) as an oil which was used without further purification.

υ_{max} (film)/cm^{-1} 2950, 1745, 1680, 840; δ_H (270 MHz, $CDCl_3$) 7.4-7.0 (4H, m, ArCH), 5.00 (1H, t, *J* 4 Hz, CH=C($OSiMe_3$)-), 4.52 (1H, s, $=CH_2$), 4.25 (1H, s, $=CH_2$), 3.55 (3H, s, $-CO_2CH_3$), 3.40 (2H, d, *J* 4 Hz, $C\underline{H}_2$-CH=$COSiMe_3$), 3-2.6 (2H, m, $-C\underline{H}_2-C=CH_2$), 1.2 (3H, s, $-CH_3$), 0.0 (9H, s, $-Si(CH_3)_3$); *m/z* (E.I.) 330 (M^+, 100), 199 (90).

Methyl 1-(2'-methylprop-2'-enyl)-2-oxo-1,2-dihydro-1-napthalenecarboxylate **(244)**

A solution of silyl enol ether **(243)** (0.7 g, 2 mmol) in 1:1 CH_2Cl_2/CH_3CN (4 ml) was added dropwise to a solution of palladium (II) acetate (0.5 g, 2.4 mmol) in acetonitrile (15 ml) and the resulting brown suspension was stirred under nitrogen for 6h. The solvent was removed under reduced pressure and the residue taken up in hexane (20 ml) and palladium metal was removed by filtration through celite. The filtrate was washed with ice cold 5% HCl (aq), saturated $NaHCO_3$ (aq), dried ($MgSO_4$) and solvent removed under reduced pressure to give a brown oil. Purification by flash column chromatography with ethyl acetate/petrol as eluent yielded the *enone* **(244)** (0.12 g, 23%) as colourless cubes, m.p. 92-93°C (from ether-petrol) (Found: C, 75.0; H, 6.26; $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.29%) υ_{max} ($CHCl_3$)/cm^{-1} 2940, 1740, 1660, 770; δ_H ($CDCl_3$, 270 MHz) 7.47 (1H, d, *J* 10 Hz - COCH=C$\underline{H}$-), 7.43-7.34 (4H, m, ArCH), 6.23 (1H, d, *J* 10 Hz, -COC$\underline{H}$=CH), 4.54 (1H, m, $=CH_2$), 4.34 (1H, m, $=CH_2$), 3.61 (3H, s, $-CO_2CH_3$), 3.3 (1H, d, *J* 13 Hz $-C\underline{H}_2-C=CH_2$), 3.1 (1H, d, *J* 13 Hz, $-C\underline{H}_2-C=CH_2$), 1.3 (3H, s, $-CH_3$); *m/z* (E.I.) 256 (M^+, 100%), 228 (50).

Methyl 1-(3'-bromo-2'-methylprop-2'-enyl)-2-oxo-1,2-dihydro-1-naphthalenecarboxylate **(246)**

The enone was prepared according to the one-pot procedure of Reich[190]. The β-keto ester **(239)** (1 g, 3 mmol) in THF (5 ml) was added to a suspension of potassium hydride (0.49 g (35%), 3.3 mmol) in THF (5 ml) and stirred at 0°C for 0.5h. Phenylselenylbromide (0.78 g, 3.3 mmol) in THF (5 ml) was added dropwise. After 0.5h at 0°C, the reaction was stirred at room temperature for 3h. The solution was cooled to 0°C and water (2 ml) and acetic acid (0.4 ml) were added followed by slow addition of 30% H_2O_2 (1.5 ml). After stirring at room temperature for 0.5h, the reaction was quenched with saturated $NaHCO_3$ (aq) (5 ml) and extracted with dichloromethane (3 x 10 ml). Drying and removal of solvent under reduced pressure to yield an oil which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the *enone* **(246)** (0.46 g, 46%) as colourless needles m.p. 95-96°C (from ether-petrol) (Found: C, 57.2; H, 4.30; $C_{16}H_{15}BrO_3$ requires C, 57.3; H, 4.51%). υ_{max} ($CHCl_3$)/cm^{-1} 2920, 1730, 1650; δ_H (270 MHz, $CDCl_3$) (7:3 mixture of isomers) 7.48 (1H, d, *J* 10 Hz, -CO-CH=C<u>H</u>-), 7.5-7.3 (4H, m, ArCH), 6.3 (0.3H, d, *J* 10 Hz, -CO-CH-), 6.25 (0.7H, d, *J* 10 Hz, -CO-CH-), 5.78 (0.3H, m, =CHBr), 5.62 (0.7H, m, =CHBr), 3.61 (2.1H, s, $-CO_2CH_3$), 3.60 (0.9H, s, $-CO_2CH_3$), 3.37 (1H, d, *J* 15 Hz), 3.12 (1H, d, *J* 15 Hz), 1.34 (0.9H, s, $-CH_3$), 1.3 (2.1H, s, $-CH_3$); *m/z* (C.I.) 337, 335 (MH^+, 30%), 255 (100).

Methyl 1-(3'-bromo-2'-methylprop-2'enyl)-2-oxo-3-phenylseleno-1,2,3,4-tetrahydro-1-naphthalenecarboxylate **(247)**

Phenylselenylchloride (0.2 g, 1 mmol) in dichloromethane (2 ml) was added to a solution of silyl enol ether **(240)** (0.4 g, 1 mmol) in dichloromethane (2 ml)

at -78°C. After 0.5h, the reaction was allowed to warm to room temperature. After 4h, the reaction mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the α-*selenoketone* **(247)** (0.28 g, 56%) as an oil. υ_{max} ($CHCl_3$)/cm^{-1} 2940, 1750, 1220, 730; δ_H (270 MHz, $CDCl_3$) (mixture of 4 isomers) 8.0-7.0 (9H, m, ArCH), 5.7 (1H, m, =CHBr), 3.6 (3H, m, -CO_2CH_3), 3.5-2.2 (5H, m), 1.7 (3H, m, -CH_3); *m/z* (C.I.) 493 (MH^+, 50%), 413 (MH^+-HBr, 30), 337 (MH^+-SePh, 90%). This material was not further characterised by microanalysis or high resolution mass spectrometry.

The β-keto ester **(239)** (1.4 g, 4 mmol) in THF (8 mmol) was added to a solution of LDA (4.5 mmol) in THF (4 ml) at -78°C. After 1h, phenylselenylchloride (0.9 g, 4.5 mmol) in THF (6 ml) was added and the mixture allowed to warm to room temperature for 4h. The reaction was quenched with dil HCl (5 ml) and extracted with ether (3 x 10 ml), dried ($MgSO_4$) and solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the α-*selenoketone* **(247)** (1 g, 65%).

Methyl 2-Hydroxy-1-naphthalenecarboxylate **(248)**

The enone **(246)** (0.17 g, 0.5 mmol), palladium (II) acetate (11 mg, 0.05 mmol), triphenylphosphine (26 mg, 0.1 mmol) and triethylamine (0.14 ml, 1 mmol) in acetonitrile (4 ml) were stirred at room temperature under nitrogen for 0.25h and then heated to reflux for 8h. After cooling, the mixture was washed with 5% HCl (aq) (3 ml), dried ($MgSO_4$) and solvent removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the *hydroxy ester* **(248)** (24 mg, 23%) as colourless needles m.p. 77-78°C (from ether) [Lit[205] 80°C]

υ_{max} ($CHCl_3$)/cm^{-1} 3200 (br), 2940, 1720, 1680, 1350; δ_H (270 MHz, $CDCl_3$) 12.28 (1H, s, -OH), 8.74 (1H, d, *J* 9 Hz), 7.90 (1H, d, *J* 9 Hz), 7.75 (1H, d, *J* 8 Hz), 7.55 (1H, m), 7.40 (1H, m), 7.16 (1H, d, *J* 9 Hz), 4.11 (3H, s, $-CO_2CH_3$); *m/z* (E.I.) 202 (M^+, 100%), 170 (80).

A solution of AIBN (5 mg) and tributyltin hydride (0.15 ml, 0.55 mmol) in toluene (5 ml) was added dropwise over 0.5h to a refluxing solution of the enone (**246**) (0.17 g, 0.5 mmol) in toluene (25 ml) and the reaction was heated for a further 6h. After cooling, the solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the *hydroxy ester* (**248**) (0.09 g, 88%) as colourless needles.

Methyl 11-methyl-13-oxotricyclo[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraene-1-carboxylate (**245**)[175]

The title compound was prepared using the procedure of Kozikowski[175]. To a solution of methyl 2-oxotetralin-1-carboxylate (**230**)[181] (4 g, 19.6 mmol), obtained by carbomethoxylation of 2-tetralone, in CH_2Cl_2 (50 ml) was added methacrolein (2.4 ml, 29.4 mmol) and 1,1,3,3-tetramethylguanidine (3.7 ml, 29.4 mmol) and stirred for 4h. The mixture was diluted with 2M HCl (20 ml) and the layers separated. The organic phase was washed with 2M HCl (2 x 10 ml) and then dried (Na_2SO_4) and solvent removed to yield the *alcohol* (**255**) (5.1 g, 95%) as a pale brown foam. υ_{max} (film)/cm^{-1} 3500, 2930, 1730; δ_H (270 MHz, $CDCl_3$)(mixture of isomers) 7.2 (3H, m, ArCH), 6.7 (1H, m, ArCH), 3.80 (1.7H, s, $-CO_2CH_3$), 3.73 (1.3H, s, $-CO_2CH_3$), 3.6-3.2 (3H, m, -CH-CO-, CH_2-Ar), 3.0 (0.7H, t, *J* 6 Hz, -C<u>H</u>OH-), 2.75 (0.3H, m, -C<u>H</u>OH-), 2.0-1.4 (4H, m, -OH, -C<u>H</u>$_2$-C<u>H</u>(CH_3)-), 1.0 (1.7H, d, *J* 6 Hz, -CHC<u>H</u>$_3$), 0.91 (1.3H, d, *J* 6 Hz, -CHC<u>H</u>$_3$); *m/z* (E.I.) 274 (M^+, 50%), 256 (100).

To a solution of the crude alcohol (**255**) (5.1 g, 18.6 mmol) in CH_2Cl_2 (25 ml) at 0°C was added triethylamine (2.8 ml, 20.5 mmol), methanesulphonyl chloride (1.6 ml, 20.6 mmol) and DMAP (0.2 g, 2 mmol) and stirred for 1h. The reaction mixture was poured into ice cold 2M HCl (20 ml) and the layers separated. The organic phase was dried (Na_2SO_4) and solvent removed under reduced pressure to yield the *mesylate* (6.5 g, 100%) as a brown gum. υ_{max} (film)/cm^{-1} 2920, 1730, 1460; δ_H (270 MHz, $CDCl_3$) 7.2 (3H, m, ArCH), 6.8 (1H, m, ArCH), 4.63 (0.4H, dd, *J* 7, 4 Hz, -CHOMs), 3.8 (1.8H, s, $-CO_2CH_3$), 3.75 (1.2H, s, $-CO_2CH_3$), 3.6-3.3 (3H, m, $-CH_2$-Ar, -CHCO-), 3.09 (1.8H, s, $-OSO_2CH_3$), 3.06 (1.2H, s, $-OSO_2CH_3$), 2.2-1.6 (3H, m, -C<u>H</u>(CH_3)-C<u>H_2</u>-), 1.03 (1.8H, d, J 6 Hz, $-CH_3$), 0.95 (1.2H, d, *J* 6 Hz, $-CH_3$); *m/z* (C.I.) 353 (80%, MH^+), 257 (100).

The crude mesylate (6.5 g, 18.5 mmol) and anhydrous sodium acetate (3.8 g, 39 mmol) in dry acetic acid (50 ml) were heated to reflux for 18h. After cooling, the solvent was removed under reduced pressure to give a residue which was partitioned between CH_2Cl_2 (40 ml) and saturated $NaHCO_3$ (aq) (30 ml). The layers were separated and the organic phase washed with saturated $NaHCO_3$(aq) (3 x 30 ml) and saturated brine (aq) (30 ml) and dried ($MgSO_4$). Removal of solvent under reduced pressure yielded an oil which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the β-*keto ester* (**245**) (2.4 g, 51%) as colourless cubes m.p. 95-96°C (from ether-petrol) υ_{max} ($CHCl_3$/cm^{-1}) 2920, 1730, 1420, 1220; δ_H (270 MHz, $CDCl_3$) 7.26-7.22 (2H, m, ArCH), 7.1 (1H, m, ArCH), 6.9 (1H, m, ArCH), 5.35 (1H, m, -C=CH-), 3.74 (3H, s, $-CO_2CH_3$), 3.43-3.38 (2H, m, $-CH_2$-Ar, =CH-C<u>H_2</u>), 3.17-3.11 (2H, m, =CH-C<u>H_2</u>, -CO-CH-), 2.6 (1H, d, *J* 17.4 Hz, $-CH_2$-Ar), 1.58 (3H, s, $-CH_3$); *m/z* (E.I.) 256 (M^+, 100%), 241 (45), 224 (60).

Tributyltin hydride (0.18 ml, 0.67 mmol) and AIBN (10 mg) in toluene (8 ml) were added dropwise over 0.5h to a refluxing solution of the α-selenoketone (**247**) (0.3 g, 0.6 mmol) in toluene (50 ml) and the reaction was heated for 4h. After cooling the solvent was removed under reduced pressure. The residue was purified by flash column chromatography on silica gel with ethylacetate-petrol as eluent to yield the β-*keto ester* (**245**) (82 mg, 53%) and the reduced material (**239**) (100 mg, 45%).

Methyl 13-hydroxy-11-methyltricyclo[7,3,1,$0^{2,7}$]-tridecaca-2(7),3,5,11-tetraene-1-carboxylate (**256**)

To a solution of β-keto ester (**245**) (0.52 g, 2 mmol) in dry methanol (5 ml) at 0°C was added sodium borohydride (38 mg, 1 mmol) and the mixture was stirred for 1h. The reaction was quenched by addition of water (2 ml) and extracted with CH_2Cl_2 (5 ml). Drying (Na_2SO_4) and removal of solvent under reduced pressure yielded the *alcohol* (**256**) (0.43 g, 84%) as a pale yellow oil which was used without further purification. υ_{max} (film)/cm^{-1} 3440, 2900, 1740, 1220; δ_H (270 MHz, $CDCl_3$) (3:2 mixture of isomers) 7.16-7.08 (4H, m, ArCH), 5.36 (0.6H, m, =CH-), 5.29 (0.4H, m, -CH=), 4.48 (0.4H, m, -C<u>H</u>OH), 4.21 (0.6H, d, *J* 4.5 Hz, -C<u>H</u>OH), 3.87 (1.8H. s. $-CO_2CH_3$), 3.76 (1.2H, s, $-CO_2CH_3$), 3.4 (0.6H, dd, *J* 18, 6 Hz), 3.25 (0.4H, dd, *J* 18, 6 Hz), 3.0-2.4 (3H, m), 2.25 (0.6H, d, *J* 18 Hz), 2.12 (0.4H, d, *J* 18 Hz), 1.60 (1.2H, s, $-CH_3$), 1.53 (1.8H, s, $-CH_3$), δ_C (68 MHz, $CDCl_3$) 177, 175 (q), 138 (q), 135 (q), 133.2 (q), 129.4 (t), 127.6 (t), 126.8 (t),. 123.3 (t), 119.7 (t), 69.7 (t), 52.2, 52.0 (p), 43.1 (s), 36.9, 36.0 (t), 29.8 (s), 22.8, 22.3 (p); *m/z* (E.I.) 258 (M^+, 100%), 240 (80), 181 (90).

Methyl 13-Acetoxy-11-methyltricyclo[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraene-1-carboxylate (**257**)

The alcohol (**256**) (1.2 g, 4.7 mmol), acetic anhydride (0.65 ml, 7 mmol), triethylamine (0.96 ml, 7 mmol) and DMAP (50 mg, 0.47 mmol) were stirred under a nitrogen atmosphere for 18h. The reaction mixture was suspended between ether (10 ml) and dil HCl (aq) (10 ml). The organic phase was washed with saturated $NaHCO_3$ (aq) and dried (Na_2SO_4). Removal of solvent under reduced pressure gave an oil which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the *acetate* (**257**) (1.09 g, 77%) as colourless cubes. m.p. 139-141°C (from ether-petrol) (Found: C, 72.0; H, 6.74. $C_{18}H_{20}O_4$ requires C, 72.0; H, 6.71%) υ_{max} ($CHCl_3$)/cm^{-1} 2900, 1730, 1235.

Major isomer (R_f 0.44, 20% ethyl acetate-petrol) δ_H (270 MHz, $CDCl_3$) 7.2-7.0 (4H, m, ArCH), 5.44 (1H, d, J 5 Hz, -CHOAc), 5.29 (1H, m, vinyl CH), 3.7 (3H, s, $-CO_2CH_3$), 3.4-3.2 (2H, m, $-CH_2$-Ar, =CH-C<u>H</u>$_2$-), 2.8 (1H, m, -C<u>H</u>-CH=), 2.5 (1H, d, *J* 16 Hz, $-CH_2Ar$), 2.1 (1H, m, =CH-C<u>H</u>$_2$-), 1.99 (3H, s, C<u>H</u>$_3CO_2$-), 1.53 (3H, s, $-CH_3$).

Minor isomer (R_f 0.36, 20% ethyl acetate-petrol)(from mixture) δ_H (270 MHz, $CDCl_3$) 7.4-7.0 (4H, m, -ArCH), 5.56 (1H, brs, -CHOAc), 5.25 (1H, m, vinyl CH), 3.66 (3H, s, $-CO_2CH_3$), 3.4-2.1 (5H, m), 2.02 (3H, s, CH_3CO_2-), 1.58 (3H, s, $-CH_3$); *m/z* (mixture)(E.I.) 300 (M^+, 20%), 240 (70), 181 (100).

13-Acetoxy-11-methyltricyclo[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraene-1-carboxylic acid (**258**)

The acetate (**257**) (1.5 g, 5 mmol)(mixture of diastereomers) and lithium iodide (2.68 g, 20 mmol) were heated to reflux in pyridine (10 ml) under a nitrogen atmosphere for 20h. After cooling, the mixture was partitioned

between CH_2Cl_2 (25 ml) and 5% HCl (aq) (10 ml). After separating the layers, the organic phase was washed with 5% HCl (aq) (5 x 10 ml), dried (Na_2SO_4) and solvent removed under reduced pressure to give a gum. Purification by flash column chromatography on silica gel with ethyl acetate as eluent yielded the *acid* **(258)** (0.58 g, 41%, 81%, based on recovered starting material) as a pale yellow foam. υ_{max} ($CHCl_3$) 2800 (br), 1740, 1220. Minor isomer (R_f 0.57, ethyl acetate) δ_H (270 MHz, $CDCl_3$) 7.2-7.0 (4H, m, ArCH),5.67 (1H, brs, -CH-OAc), 5.23 (1H, m, -C<u>H</u>=C), 3.3 (1H, dd, *J* 17, 5 Hz, -CH_2-Ar), 3.0-2.7 (3H, m), 2.14 (1H, d, *J* 17 Hz), 2.06 (3H, s, CH_3CO_2-), 1.60 (3H, s, -CH_3).

Major isomer (from 3:2 mixture)δ_H (270 MHz, $CDCl_3$) 7.2-7.0 (4H, m, ArCH), 5.45 (1H, d, *J* 5 Hz -CHOAc), 5.34 (1H, m, -CH=C), 3.4-2.3 (5H, m), 1.99 (3H, s, CH_3CO_2-), 1.53 (3H, s, -CH_3); δ_C (68 MHz, $CDCl_3$) (3:2 mixture of isomers) 180 (q), 170.9 (q), 137.7 (q), 135.4 (q), 134.2 (q), 133.5 (q), 132.5 (q), 129.1 (t), 127.2 (t), 126.5, 126.0 (t), 122.6 (t), 119.9 (t), 72.7,72.6 (t), 44.4 (s), 37.7 (s), 35.5 (s), 33.8 (t), 32.9 (t), 30.3 (s), 23.0, 22.6 (p), 21.2, 21.1 (p); *m/z* (E.I.) 286 (M^+, 5%) 181 (50).

13-Iodo-11-methyltricyclo[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraene-1-carboxylic acid **(259)**

The acetate **(257)** (0.99 g, 3.3 mmol) and lithium iodide (0.88 g, 6.6 mmol) in 2, 6-lutidine were heated to reflux for 4h. Work up as for preparation of carboxylic acid **(258)** gave a foam which was purified by flash column chromatography on silica gel with methanol/ethyl acetate as eluent to yield the *acid* **(259)** (0.65 g, 56%) as a pale brown foam. υ_{max} ($CHCl_3$)/cm^{-1} 2900, 1720. δ_H (270 MHz, $CDCl_3$) 7.2-7.0 (4H, m, ArCH), 5.30 (1H, m, -CH=C-), 3.25 (1H, dd, *J* 17, 5 Hz), 3.0-2.0 (5H, m), 1.6 (3H, s, -CH_3). δ_C (68 MHz, $CDCl_3$). 180.1 (q), 138.1 (q), 133.5 (q), 132.8 (q), 129.3 (t), 127.3 (t), 126.6

(t), 126.5 (t), 119.9 (t), 36.9 (s), 36.7 (t), 35.9 (s), 23.1 (p), 19.4 (t); *m/z* (E.I.) 226 (M^+-I, 10%), 181 (60).

13-Acetoxy-11-methyltricyclo[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraene-1-carbonylchloride **(260)**

The carboxylic acid **(258)** (0.24 g, 0.8 mmol) as a mixture of diastereomers in CH_2Cl_2 (2 ml) was stirred with oxalyl chloride (0.1 ml, 1.2 mmol). One drop of DMF was added and gas evolved. After 0.5h, the solvent was removed under reduced pressure to yield the *acid chloride* **(260)** (0.24 g, 98%) as a pale brown solid. υ_{max} ($CHCl_3$)/cm^{-1} 2900, 1800, 1740, 1220; δ_H (270 MHz, $CDCl_3$) (3:2 mixture of isomers) 7.3-7.0 (4H, m, ArCH), 5.7 (0.4H, m, -C<u>H</u>OAc), 5.57 (0.6H, d, *J* 5 Hz, -CHOAc), 5.34 (0.6H, m, =CH-), 5.25 (0.4H, m, =CH-), 3.5-2.5 (5H, m), 2.08 (1.2H, s, CH_3CO_2-), 2.03 (1.8H, s, CH_3CO_2-), 1.59 (1.2H, s, -CH_3), 1.55 (1.8H, s, -CH_3); *m/z* (E.I.) 268 (M^+-HCl, 5%), 181 (100). This compound was not further characterised by microanalysis or high resolution mass spectrometry.

13-Acetoxy-11-methyltricylco[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraenecarbonyl azide **(261)**

A solution of the acid chloride **(260)** (0.52 g, 1.7 mmol) in acetone (10 ml) was cooled to 0°C. Sodium azide (0.12 g, 1.87 mmol) in water (1 ml) was added dropwise and the mixture stirred for 0.5h. The reaction was further diluted with ice cold water (5 ml) added dropwise to precipitate the product. After 0.5h, ether (10 ml) was added and the layers separated. The organic phase was dried (Na_2SO_4) and solvent removed under reduced pressure to yield the *acyl azide* **(261)** (0.5 g, 94%) as a colourless solid which was used without further purification. υ_{max} ($CHCl_3$)/cm^{-1} 2900, 2120, 1740, 1700, 1220.

13-Acetoxy-1-isocyanato-11-methyltricyclo[7,3,1,$0^{2,7}$]trideca-2(7),3,5,11-tetraene (**262**)

The acyl azide (**261**) (0.52 g, 1.7 mmol) was heated to reflux in toluene for 1h. After cooling, solvent was removed under reduced pressure to yield the *isocyanate* (**262**) (0.48 g, 100%) as an oil which was used without further purification. υ_{max} (film)/cm^{-1} 2900, 2250, 1740, 1240; δ_H (270 MHz, $CDCl_3$) 7.55-7.06 (4H, m, ArCH), 5.5-5.2 (2H, m, -CHOAc, =CH-), 3.4-2.2 (5H, m), 2.17 (1.8H, s, CH_3CO_2-), 2.08 (1.2H, s, CH_3CO_2-), 1.57 (1.8H, s, -CH_3), 1.52 (1.2H, s, -CH_3); *m/z* (E.I.) 283 (M^+, 30%), 241 (100).

13-Acetoxy-(N-methoxycarbonyl)-11-methyltricyclo[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraenylamine (**263**)

The isocyanate (**262**) (0.15 g, 0.05 mmol) in dry methanol (2 ml) was heated to reflux for 6h. Solvent was removed under reduced pressure and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the *carbamate* (**263**) (0.08 g, 51%) as colourless cubes m.p. 190-192°C (from ether-petrol). υ_{max} ($CHCl_3$)/cm^{-1} 3400, 2920, 1740, 1220; δ_H (270 MHz, $CDCl_3$) (3:2 mixture of isomers) 7.4-7.0 (4H, m, ArCH), 5.8-5.3 (2H, m, -CHOAc, =CH-), 3.86 (1.8H, s, CH_3O-), 3.76 (1.2H, s, CH_3O-), 3.5-2.5 (5H, m), 2.1 (1.8H, s, CH_3CO_2-), 2.08 (1.2H, s, CH_3CO_2-), 1.60 (1.2H, s, -CH_3), 1.56 (1.8H, s, -CH_3), δ_C (68 MHz, $CDCl_3$) 133, 131 (q), 129.6, 129.3, 129.2, 128.7, 127.7, 126.9, 126.3 (t); 127.6, 125.2 (q), 124.4, 123.4 (t), 70.7, 70.1 (t), 52.5, 52.4 (p), 36.9, 35.7 (t), 35.9, 35.1 (s), 22.8, 22.5 (s), 20.9, 20.5 (s); *m/z* (E.I.) 315 (M^+, 20%), 258 (60), 181 (100).

13-Acetoxy-11-methyl-N-(2'-trimethylsilylpropioloyl)-tricyclo-[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraenylamine **(265)**

Magnesium turnings (48 mg, 2 mmol) in THF (4 ml) were stirred with 1,2-dibromoethane (0.1 ml). After initiation, 1,1-bromotrimethylsilylethene[195] (0.36 g, 2 mmol) in THF (1 ml) was added at a rate to maintain reflux. After the addition was completed, the reaction was maintained at reflux for 1h. After cooling to room temperature, the isocyanate **(262)** (0.3 g, 1 mmol) in THF (1 ml) was added dropwise and the reaction stirred for 4h. The reaction was quenched by addition of saturated NH_4Cl (aq) (1 ml) and partitioned between ether (10 ml) and water (10 ml). The aqueous phase was extracted with ether (2 x 10 ml). The combined organic phases were washed with saturated brine (aq) and dried ($MgSO_4$) and solvent removed under reduced pressure to give an oil. Purification by flash column chromatography on silica gel with ethyl acetate/petrol as eluent yielded the *amide* **(265)** as two separable diastereomers (0.1 g, 26% (A) and 0.11 g, 29%(B)) as colourless cubes.
Diastereomer A(R_f 0.40, 20% ethyl acetate-petrol), m.p.,125°C (decomposes) (from ether-petrol) (Found: M^+, 383.188; $C_{22}H_{29}NO_3Si$ requires 383.192), υ_{max} ($CHCl_3$)/cm^{-1} 3350, 2900, 1740, 1240, 840; δ_H (270 MHz, $CDCl_3$) 7.34-6.85 (4H, m, ArCH), 5.92 (1H, d, *J* 2 Hz, $=CH_2$), 5.70 (1H, br s, NH), 5.56 (1H, d, *J* 5 Hz, -CHOAc), 5.49 (1H, d, *J* 2 Hz, $=CH_2$), 5.10 (1H, br m, =CH-), 3.58 (1H, d, *J* 15 Hz, =CH-C<u>H</u>$_2$-), 2.8 (2H, m, -CHOAc-C<u>H</u>-, benzylic CH_2), 2.35 (1H, m, benzylic CH_2), 2.15 (1H, d, *J* 15 Hz, =CH-C<u>H</u>$_2$-), 1.98 (3H, s, CH_3CO_2-), 1.38 (3H, s, -CH_3), 0.00 (9H, s, -$Si(CH_3)_3$);δ_C (68 MHz, $CDCl_3$) 170.5 (q), 151.5(q), 140.7 (q), 133.4 (q), 131.6 (q), 129.0 (q), 128.9 (t), 127.7 (q), 126.9 (t), 126.3 (t), 124.7 (t), 123.3 (s), 121.3 (t), 71.0 (t), 42.2 (s), 35.5 (t), 35.2 (s), 22.8 (p), 21.3 (p), -1.6 (p).
Diastereomer B (R_f 0.22, 20% ethyl acetate-petrol) δ_H (270 MHz, $CDCl_3$) 7.3-7.04 (4H, m, ArCH), 6.1 (1H, d, *J* 2.2 Hz, $=CH_2$), 5.8 (1H, br s, -NH), 5.70

(1H, m, -CHOAc), 5.62 (1H, d, *J* 2.2 Hz, $=CH_2$), 5.30 (1H, br m, =CH-), 3.35 (1H, dd, *J* 15, 4 Hz), 2.9 (1H, m), 2.7 (2H, m), 2.2 (1H, d, *J* 15 Hz), 2.08 (3H, s, CH_3CO_2-), 1.57 (3H, s, $-CH_3$), 0.16 (9H, s, $-Si(CH_3)_3$); *m/z* (E.I.) 383 (M^+,100%).

13-Hydroxy-11-methyl-N-(2'-trimethylsilylpropioloyl)-tricyclo-[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11,-tetraenylamine **(268)**

To a solution of the amide **(265)** (diastereomer A) (0.16 g, 0.4 mmol) in dry methanol (2 ml) was added sodium methoxide in methanol (0.1 ml, 0.4M) and the reaction stirred at room temperature for 4h. 5% HCl (2 ml) was added and the mixture extracted with CH_2Cl_2 (3 x 5 ml). Drying (Na_2SO_4) and removal of solvent under reduced pressure gave an oil which was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent yielded the *alcohol* **(268)** (0.1 g, 76%) as colourless needles. (Found:M^+-CH_3, 326.1567; M^+-CH_3 requires 326.1576: M^+, 342.183; $C_{19}{}^{13}CH_{27}NO_2Si$ requires 342.184) υ_{max} ($CHCl_3$)/cm^{-1} 3220, 2900, 1600, 1520, 840. (R_f0.28, 20% ethyl acetate -petrol) δ_H (270 MHz, $CDCl_3$) (Diastereomer A) 7.2-6.8 (4H, m, ArCH), 6.1 (1H, br s, NH), 6.04 (1H, d, *J* 2 Hz, $=CH_2$), 5.56 (1H, d, *J* 2 Hz, $=CH_2$), 5.20 (1H, br m, =CH-), 4.36 (1H, d, *J* 4 Hz, -CHOH), 4.20 (1H, t, *J* 4,5 Hz, -CHOH), 3.2 (1H, dd, *J* 5,15 Hz), 2.6 (2H, m), 2.2 (2H, m), 1.32 (3H, s), 0.00 (9H, s), $-Si(CH_3)_3$); δ_C (68 MHz, $CDCl_3$) 175.2 (q), 152.4 (q), 139.4 (q), 136.3 (q), 132.7 (q), 131.5 (s), 130.8 (t), 128.6 (t), 128.0 (t), 127.0 (t), 125.8 t), 73.9 (t), 48,2 (s), 30.6 (t), 31.4 (s), 23.9 (p), 0.00 (p); *m/z* (E.I.) 341 (M^+, 100%).

Amide **(265)** (diastereomer B) was hydrolysed to give alcohol **(268)** using the above procedure.(R_f 0.16, 20% ethyl acetate-petrol) δ_H (270 MHz, $CDCl_3$) (Diastereomer B) 7.2-6.8 (4H, m, ArCH), 6.0 (1H, d, *J* 2 Hz, $=CH_2$), 5.8 (1H, br s, NH), 5.5 (1H, d, *J* 2 Hz, $=CH_2$), 5.1 (1H, br m, -CH=C), 4.2 (1H, br s),

3.2-2.8 (6H, m), 1.2 (3H, s, $-CH_3$), 0.00 (9H, s, $-Si(CH_3)_3$).

13-Imidazoylthiocarbonyloxy-11-methyl-N-(2'-trimethylsilylpropioloyl)-tricyclo-trideca-2(7),3,5,11-tetraenylamine **(269)**

Solid thiocarbonyldiimidazole (0.16 g, 0.88 mmol) was added to a solution of the alcohol **(268)** (diastereomer A) (0.15 g, 0.43 mmol) in 1,2-dichloroethane and the mixture heated to reflux for 5h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the *alkoxythiocarbonylimidazolide* **(269)** (0.15 g, 77%) as an oil. υ_{max} ($CHCl_3$)/cm^{-1} 2920, 1640, 1240, 1100, 840;(R_f 0.33, 40% ethyl acetate-petrol)δ_H (270 MHz, $CDCl_3$) (diastereomer A) 7.9 (1H, s, ImCH), 7.4-6.9 (6H, m, ArCH, ImCH), 6.62 (1H, d, *J* 5 Hz, -C<u>H</u>OCS-), 6.0 (1H, d, *J* 2 Hz, $=CH_2$), 5.97 (1H, br s, NH), 5.58 (1H, d, *J* 2 Hz, $=CH_2$), 5.28 (1H, br m, -CH=C), 3.9 (1H, d, *J* 17 Hz), 3.3 (1H, m), 3.0 (1H, dd, *J* 17, 6 Hz), 2.6 (1H, d, *J* 12 Hz), 2.15 (1H, d, *J* 7 Hz), 1.5 (3H, s, $-CH_3$), 0.0 (9H, s, $-Si(CH_3)_3$); *m/z* (C.I.) 452 (MH^+, 10%), 324 (25%).

Alcohol **(268)** (diastereomer B) was also converted to the *alkoxythiocarbonylimidazolide* **(269)** (diastereomer B) (R_f 0.27%, 40% ethyl acetate-petrol) δ_H(270 MHz, $CDCl_3$) 8.21 (1H, s, ImCH), 7.58 (1H, s, ImCH), 7.35-7.0 (5H, m, ArCH, ImCH), 6.6 (1H, m, -C<u>H</u>OCS-), 6.0 (2H, m, -NH, $=CH_2$), 5.6 (1H, d, *J* 2 Hz, $=CH_2$), 5.32 (1H, br m, -CH=C-), 3.4 (1H, dd, *J* 15, 6 Hz), 3.2 (1H, br s), 2.8 (2H, m), 2.28 (1H, d, *J* 15 Hz), 1.60 (3H, s, $-CH_3$), 0.00 (9H, s, $-Si(CH_3)_3$).

11-Methyl-13-p-toluenesulphonyloxy-N-(2'-trimethylsil ylpropioloyl)-tricyclo-[7,3,1,$0^{2,7}$]-trideca-2(7),3,5,11-tetraenylamine (**271**)

A solution of the alcohol (**268**) (0.1 g, 0.3 mmol)(diastereomer B) in chloroform (2 ml) was cooled to 0°C. p-Toluenesulphonylchloride (0.09 g, 0.45 mmol) and pyridine (0.05 ml, 0.6 mmol) were added and the mixture stirred for 18h. The reaction was diluted with ether (5 ml) and water added (1 ml). The layers were separated and the organic phase washed with dil HCl (aq) and saturated $NaHCO_3$ (aq). After drying (Na_2SO_4) and removal of solvent under reduced pressure, the residue was purified by flash column chromatography on silica gel with ethyl acetate/petrol as eluent to yield the *tosylate* (**268**) (0.09 g, 65%) as a colourless solid. υ_{max} ($CHCl_3$)/cm^{-1} 2900, 1640, 1440, 1360, 840; δ_H (270 MHz, $CDCl_3$), 7.67 (2H, d, *J* 8 Hz, ArCH), 7.2-6.7 (6H, m, ArCH), 5.75 (2H, br m, -NH, $=CH_2$), 5.40 (1H, d, *J* 2 Hz, $=CH_2$), 5.30 (1H, d, *J* 5 Hz, -CHOTs), 5.00 (1H, br m, -CH=C), 3.3 (1H, d, *J* 17 Hz), 3.0-2.5 (4H, m), 2.22 (3H, s, -Ar-CH_3), 1.30 (3H, s, -CH_3), 0.00 (9H, s, -Si(CH_3)$_3$); *m/z* (C.I.) 496 (MH^+, 5%), 384 (100).

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